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selected medicinal plants

Volume 3

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Introduction

Increasing role of the WHO monographs on selected medicinal plants

Since 1999, WHO has published two volumes of the *WHO monographs on selected medicinal plants*. Volume 1 includes 28 monographs and volume 2 contains an additional 30 monographs. Both of these volumes are now available on the WHO web site http://www.who.int/medicines/organization/trm/orgtrmstrat.htm).

Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role. For example, in the recent WHO global survey on national policy and regulation of herbal medicines, of the 34 countries reporting that they do not have their own national monographs and use other monographs, 13 use the WHO monographs as an authoritative reference. Moreover, the format of the WHO monographs continues to be commonly used for developing national monographs. In the same survey, of the 46 countries that have already developed national monographs on herbal medicines, several countries, such as Armenia, Bhutan, Brazil, Malaysia, and Myanmar, reported having used the WHO format as a basis.

In May 2002, WHO launched its Traditional Medicine Strategy covering the period 2002–2005. In 2003, the World Health Assembly adopted resolution WHA56.31 on traditional medicine, which requests WHO to seek, together with WHO collaborating centres, evidence-based information on the quality, safety and cost-effectiveness of traditional therapies. The objective is to provide guidance to Member States on the definition of products to be included in national directives and proposals on traditional-medicine policy implemented in national health systems. The continued development of the *WHO monographs on selected medicinal plants* is one of the important activities being undertaken to meet the demands from Member States and in the implementation of the WHO Traditional Medicine Strategy.

Preparation of monographs for volume 3

During the preparation of volume 3, more than 170 experts were involved, in addition to members of WHO's Expert Advisory Panel on Traditional

Medicine, a significant expansion in comparison to the numbers involved in the first two volumes. National drug regulatory authorities in 65 countries participated in the process, again a greater number than for the previous volumes. This global network of active players facilitated wider access to the available scientific references and information, in terms of both quality and quantity. This considerable level of support contributed greatly to the efficiency of the preparation process.

The Third WHO Consultation on Selected Medicinal Plants was held in Ottawa, Canada, in July 2001 to review and finalize the draft monographs. Thirty-two experts and drug regulatory authorities from WHO Member States participated (Annex 1). Following extensive discussion, 31 of the 33 draft monographs were adopted for inclusion.

At the subsequent tenth International Conference of Drug Regulatory Authorities held in China, Hong Kong Special Administrative Region in June 2002, the 31 draft monographs adopted for volume 3 of the *WHO monographs on selected medicinal plants* were presented. In its recommendations, the Conference requested WHO to publish them as soon as possible.

Selection of medicinal plants

The selection of medicinal plants for inclusion in the WHO monographs is based on worldwide use. The medicinal plants selected must meet two major criteria: (1) they must be in common use in at least two WHO Regions; and (2) there must be sufficient scientific data available to satisfy the requirements of the various sections in the monograph format.

The Third WHO Consultation on Selected Medicinal Plants discussed the selection criteria and made recommendations that will be applied starting with the preparation of volume 4 of the WHO monographs.

Changes in format in volume 3

Following intensive discussion at the Ottawa Consultation the title and context of the three categories included in the section Medicinal uses has been changed. The changes are described in the in the General technical notices.

It was also decided at the Ottawa Consultation that the section on Adverse reactions should be moved to follow immediately after the section on Pharmacology, to provide a more logical progression for the subsequent sections on Contraindications, Warnings and Precautions.

A description of selected sections of the monographs is given in the General technical notices, which reflect the above-mentioned format changes. For easy reference, two cumulative indexes are provided as an-

nexes. Annex 2 lists the monographs in alphabetical order of the plant name, while Annex 3 is according to the plant materials of interest.

Under the section "Geographical distribution", an attempt has been made to describe the geographical distribution of the plant, i.e. its natural distribution, where it is cultivated, and conditions of cultivation, harvesting and storage. This has been a challenge, owing to the lack of data based on established national good agricultural practices and/or good collection practices for medicinal plants. In 2003, WHO published the *WHO guidelines on good agricultural and collection practices* (*GACP*) *for medicinal plants*, which provide general technical guidance on obtaining medicinal plant materials of good quality for the sustainable production of herbal medicines in the overall context of quality assurance and control of herbal medicines. It is hoped that these guidelines will facilitate the development of GACP monographs on specific medicinal plants at national level, which in turn should bridge the current information gap in this area.

Purpose and content of monographs

The purpose of the monographs was clearly explained in the introduction to volume 1, and it is unnecessary to repeat it here. But I would like to emphasize again that the word "monograph" is used as a technical term only. It does not have the same meaning as "monograph" in any type of pharmacopoeia. In addition, I must reaffirm that this publication is not intended to replace any official compendia such as pharmacopoeias, formularies or legislative documents.

It should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO's official endorsement or approval. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.

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General technical notices

These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO's Member States; to provide models to assist WHO's Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO's Member States.

The format used for volume 3 essentially follows that of volume 2. However, to keep relevant sections together, *Adverse reactions* appears immediately after the section on *Pharmacology*. The titles of three categories under the *Medicinal uses* have been changed to the following:

- *Uses supported by clinical data*
- *Uses described in pharmacopoeias and well established documents*
- *Uses described in traditional medicine*

The *Definition* provides the Latin binomial name, the most important criterion in quality assurance. Latin binomial synonyms and vernacular names, listed in *Synonyms* and *Selected vernacular names* respectively, are names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Code of Botanical Nomenclature. The vernacular names comprise an alphabetical list of selected names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. They refer to the medicinal plant itself not the medicinal plant part, which is identical to the monograph name. The lists are not complete, but reflect the names of the concerned medicinal plant appearing in the official monographs and reference books consulted and those in the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, Chicago, IL, USA). While every effort has been made to delete names referring to the

medicinal plant part, the relevant section of each monograph may still include these.

Geographical distribution is not normally found in official compendia, but is included here to provide additional quality assurance information. The detailed botanical description under *Description* is intended for quality assurance at the stages of production and collection; the description of the crude drug material under *Plant material of interest* is for the same purpose at the manufacturing and commerce stages.

General identity tests, *Purity tests* and *Chemical assays* are all normal compendial components included under those headings in these monographs. Where purity tests do not specify accepted limits, those limits should be set in accordance with national requirements by the appropriate authorities of Member States.

Each medicinal plant and the specific plant part used as crude drug material contain active or major chemical constituents with a characteristic profile that can be used for chemical quality control and quality assurance. These constituents are described in the *Major chemical constituents*.

Descriptions included in *Medicinal uses* should not be taken as implying WHO's official endorsement or approval for such uses. They merely represent the systematic collection of scientific information available at the time of preparation, for information exchange.

The first category, *Uses supported by clinical data*, includes medical indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. Clinical trials may be controlled, randomized, double-blind studies, open trials, cohort studies or well documented observations on therapeutic applications.

The second category, *Uses described in pharmacopoeias and well established documents*, includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or governmental monographs. Uses having a pharmacologically plausible basis are also included, as well as information resulting from clinical studies that clearly need to be repeated because of conflicting results.

The third category, *Uses described in traditional medicine*, refers to indications described in unofficial pharmacopoeias and other literature, and to traditional uses. Their appropriateness could not be assessed, because sufficient data to support the claims could not be found in the literature. Traditional uses that address severe pathologies, such as cancer, AIDS, hepatitis, etc., as they relate to these modern biomedical terms, should only be included under the third heading if pharmacological data

or robust ethnopharmacological/ethnobotanical reports are available to support the claims.

The *Experimental pharmacology* section includes only the results of investigations that prove or disprove the cited medicinal uses. Abbreviated details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included, to avoid confusion.

The details included in the *References* have been checked against the original sources wherever possible. For references in languages other than English, except for those in Chinese and Japanese, the title is given in the original language, except in cases where an English summary is available.

Fructus Ammi Majoris

Definition

Fructus Ammi Majoris consists of the dried ripe fruits of *Ammi majus* L. (Apiaceae) (*1, 2*).

Synonyms

Apium ammi Crantz, *Selinum ammoides* E.H.L. Krause (*3*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Aatrilal, ammi commun, bishop's weed, bullwort, crow's foot, cumin royal, devil's carrot, gazar el-shitan, greater ammi, habab, herb william, hirz al-shayateen, khella shaitani, khellah shitany, mayweed, nounkha, qciba, rejl el-ghorab, rijl al-tair, zfenderi el maiz (*1, 2, 4–6*).

Geographical distribution

Indigenous to Egypt, and widely distributed in Europe, the Mediterranean region and western Asia. Cultivated in India (*2*).

Description

An annual, 0.9–1.5 m high with striated subglaucous stems. Leaves acutely serrulate, alternate, bipinnate, lobes oblong. Inflorescence a compound umbel with slender primary rays up to 5 cm long, scattered secondary rays 2–5 cm long, minute reticulate points; involucre of bracts 1.5–2.5 cm long; flowers bisexual, polygamous, bracteate; calyx teeth obsolete or small; petals obovate with an inflexed point, exterior petals frequently longer; stamens epigynous; ovary inferior, two-locular, stigma capitate. Fruit laterally compressed, oblong, mericarps of the cremocarp separated by a carpophore. Seed small, pendulous, albuminous (*2*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp nearly cylindrical, usually separated into its two mericarps, rarely entire, with a part of the pedicel attached. Mericarp small, slightly concave on the commissural side, slightly tapering towards the apex; 2.0–2.5 mm long, 0.75 mm wide, reddish-brownish to greenish-brown, crowned with a nectary, disc-like stylopod. Externally glabrous, rough, marked with five broad, distinct, yellowish-brown primary ridges, alternating with four equally prominent, dark brown secondary ridges. Internally comprises a pericarp with six vittae, four in the dorsal and two in the commissural side, and a large orthospermous endosperm in which is embedded a small apical embryo. Carpophore forked, each branch entering at the apex of the mericarp and uniting with the raphe (*1, 2*).

Organoleptic properties

Odour: slightly aromatic, terebinthinate; taste: aromatic, strongly pungent, slightly bitter (*1*).

Microscopic characteristics

Epidermis of the pericarp consists of polygonal cells, with straight anticlinal walls and short papillae, containing cluster or prismatic crystals of calcium oxalate, and covered with a strongly striated cuticle; stomata, occasionally of the anisocytic type, but with no trichomes. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, four in the dorsal and two in the commissural side, which appear elliptical in transverse section, each surrounded by large, radiating cells; traversed in the primary ridges by vascular bundles, which appear oval, ovoid or rounded in transverse section, not accompanied by vittae, each bundle with a xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres and reticulate, lignified cells. Innermost layer consists of large, polygonal, brown-walled cells, with thick, non-porous inner walls. Endocarp composed of narrow, tangentially elongated cells, many in regular arrangements in variously oriented groups (e.g. parquet arrangement), adhering to the brown seed coat, which is formed of similar but wider and shorter cells. Endosperm consists of polygonal, thick-walled, cellulosic parenchyma, containing fixed oil and several aleurone grains, 4–12 µm in diameter, each with one or two rounded globoid and one or two microrosette crystals of calcium oxalate, 2–5 µm in diameter. Carpophore, each branch traversed by a vascular bundle of fibres and spiral vessels (*1, 2, 7*).

Powdered plant material
Yellowish-brown and characterized by fragments of epicarp with polygonal, subrectangular or elongated, short, papillose cells, containing cluster or prismatic crystals of calcium oxalate, and covered with thick, distinctly striated cuticle. Also present are fragments of mesocarp with brownish pieces of vittae, reticulate cells, vessels and fibres; fragments of endocarpal cells with a distinct parquet arrangement, usually adhering to brown cells of the testa; numerous fragments of the endosperm containing colourless, polygonal cells, numerous oil globules and several aleurone grains, 4–12 µm in diameter, each enclosing microrosette crystals of calcium oxalate, 2–5 µm in diameter. Trichomes and starch grains absent (*1, 2*).

General identity tests
Macroscopic and microscopic examinations, microchemical tests (*1, 2*), and thin-layer chromatography for the presence of xanthotoxin and bergapten (*8*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*9*).

Total ash
Not more than 7% (*1, 2*).

Acid-insoluble ash
Not more than 0.04% (*2*).

Water-soluble extractive
Not less than 17% (*2*).

Alcohol-soluble extractive
Not less than 16% (*2*).

Loss on drying
Not more than 12% (*1*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*10*). For other pesticides, see the *European pharmacopoeia* (*10*), and the WHO guidelines on quality control methods for medicinal plants (*9*) and pesticide residues (*11*).

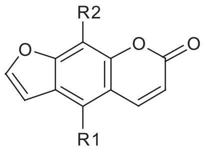
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*9*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*9*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.5% xanthotoxin, 0.3% imperatorin and 0.01% bergapten, determined by spectrophotometry (*1*). A high-performance liquid chromatography method is also available for quantitative analysis (*12*).

Major chemical constituents
The major constituents are furanocoumarins, the principal compounds being xanthotoxin (methoxsalen, 8-methoxypsoralen (8-MOP) ammoidin; up to 1.15%), imperatorin (ammidin; up to 0.75%) and bergapten (heraclin, majudin, 5-methoxypsoralen (5-MOP), up to 1.88%). Other coumarins of significance are marmesin (up to 0.25%), isoimperatorin (0.01%), heraclenin (0.07%) and isopimpinellin (0.01%). Other constituents of interest are acetylated flavonoids (*13–17*). The structures of xanthotoxin, imperatorin and bergapten are presented below.



furanocoumarins	R1	R2
bergapten	OCH_3	H
imperatorin	H	$O\text{-}CH_2\text{-}CH{=}C(CH_3)_2$
xanthotoxin	H	OCH_3

Medicinal uses
Uses supported by clinical data
Treatment of skin disorders such as psoriasis and vitiligo (acquired leukoderma) (*1, 5, 18–26*).

Uses described in pharmacopoeias and well established documents
Treatment of vitiligo (*1*).

Uses described in traditional medicine

As an emmenagogue to regulate menstruation, as a diuretic, and for treatment of leprosy, kidney stones and urinary tract infections (*6*).

Pharmacology

Experimental pharmacology

Antimicrobial and antischistosomal activities

A 50% dilution of an acetone or 95% ethanol extract of Fructus Ammi Majoris inhibited the growth of the fungus *Neurospora crassa* in vitro (*27*). Intragastric administration of 400.0 mg/kg body weight (bw) of a hot aqueous extract or 15.0 mg/kg bw of a petroleum ether extract of the fruits per day for 6 days reduced the *Schistosoma mansoni* worm burden in mice by 49.3–72.3% (*15*).

Miscellaneous effects

Intragastric administration of 500.0 mg/kg bw of the powdered fruits per day to rats for 4 weeks did not reduce the incidence of glycolic acid-induced kidney stones (*28*).

Photosensitizing effects

Xanthotoxin is available in synthetic form and is a known photosensitizing agent and antipsoriatic. The augmented sunburn reaction involves excitation of the drug molecule by radiation in the long-wave ultraviolet (UV) A range. The transfer of energy to the drug molecule produces a triplet electronic state. The excited molecule then binds covalently with cutaneous DNA, forming a cyclobutane ring with the DNA pyrimidine bases, within the epidermal cells of the skin. In this manner, xanthotoxin inhibits nuclear division and cell proliferation (*21, 22, 29*).

Toxicology

Intoxication due to the simultaneous ingestion of ergot alkaloids from *Claviceps purpurea* sclerotia and furanocoumarins from *Ammi majus* seeds was reported in pigs after ingestion of contaminated feed. Nervous system intoxication was first observed 5–7 days after the initiation of feeding of the suspect rations. This was followed by cutaneous irritation, including snout ulcers, eyelid oedema and conjunctivitis. Ten days after the feeding, eight abortions were observed and, in nursing sows, udder oedema and teat cracking were observed. Examination of the adulterated feed indicated that it contained 2.2% *A. majus* seeds and 0.14% *C. purpurea* sclerotia. Quantitative analysis showed the presence of 3.2 g of xanthotoxin and 0.65 g of imperatorin per 100 g of *A. majus* seeds, and 0.73 g of ergot alkaloids per 100 g of *C. purpurea* sclerotia (*30*).

The median lethal doses (LD_{50}) of xanthotoxin, imperatorin and bergapten injected into the ventral lymph sac of toads were 13.8 mg/100 g bw, 14.0 mg/100 g bw and 32.0 mg/100 g bw, respectively. In rats, the intramuscular LD_{50} values were 16.0 mg/kg bw, 33.5 mg/kg bw and 94.5 mg/kg bw, respectively (*31*).

After 4–8 days of administration of 2 g of *A. majus* seeds per day to 3- to 5-week-old goslings in the diet, the animals became photosensitive. Photosensitivity appeared after 4–5 hours of exposure to sunlight and was characterized by erythema, haematomas and blisters on the upper side of the beak (*32*). The photoirritant effects of five constituents of *A. majus* seeds, xanthotoxin, imperatorin, isopimpinellin, bergapten and isoimperatorin, were evaluated in the mouse-ear assay. Isoimperatorin was the most irritant compound (median irritant dose (ID_{50}) 0.0072 mg after 5 days of treatment), while imperatorin was the least irritant (ID_{50} 0.3823 mg after 6 days of treatment). The three other compounds showed minimal photoirritant activity (*33*).

Chronic toxicity in the form of decreases in the red blood cell count and haemoglobin A concentration was observed in mice after administration of 100.0 mg/kg bw of a 95% ethanol extract of the fruits in drinking-water (*34*). Administration of 6.2–18.9 g/kg bw of the fruits per day in the diet to cattle and sheep for 49 days caused photosensitization in both species (*35*). Ingestion of *A. majus* seeds together with exposure to sunlight caused mydriasis in geese and ducks (*36*). Chronic 7-week exposure of ducks and geese to the fruits (dose not specified) caused severe deformities of the beak and footwebs, mydriasis and ventral displacement of the pupils (*37, 38*). Ophthalmological examination of the animals revealed dense pigmentation in the fundus (pigmentary retinopathy) and hyperplasia of the retinal pigment epithelium (*36, 39*). The iris showed varying degrees of atrophy of the sphincter pupillae (*36*).

Intragastric administration of a single dose of 8.0 g/kg bw of the fruits to sheep produced cloudy cornea, conjunctivokeratitis, photophobia and oedema of the muzzle, ears and vulva (*40*). Intragastric administration of 2.0 g/kg or 4.0 g/kg bw per day produced similar symptoms after 72–96 hours (*40*).

Clinical pharmacology

Numerous clinical trials have assessed the efficacy of Fructus Ammi Majoris and xanthotoxin for the treatment of vitiligo, psoriasis and hypopigmentation tinea versicolor (*18–20, 41–44*).

The powdered fruits (dose not specified) were administered orally to leukodermic patients, who then exposed the affected patches to direct sunlight for 1 hour. The patients subsequently developed symptoms of

itching, redness, oedema, vesiculation and oozing in the leukodermic patches. A few days later the affected skin gradually started to display deep brown pigmentation. Repigmentation usually developed within 1 week, in a punctate or perifollicular fashion, spreading inwards from the margin or diffuse (*5*). In a small clinical trial without controls, two groups of eight patients with leukoderma were treated orally with 0.05 g of xanthotoxin three times per day or in the form of a liniment, 1 g/100 ml, applied to the skin. The patients then exposed the leukodermic areas to the sun for 0.5 hour or to UV light for 2 minutes, gradually increasing to 10 minutes, per day. After treatment, the leukodermic skin areas were inflamed and vesiculated, and were treated as second-degree burns. When healing occurred these areas began to show normal pigmentation (*19*).

Since 1966, over 100 clinical studies have investigated the safety and efficacy of xanthotoxin for the treatment of a wide range of ailments including vitiligo and psoriasis, in a variety of dosage forms and routes of administration. The drug is now accepted as standard medical therapy for the symptomatic control of severe, recalcitrant, disabling psoriasis that does not respond to other therapy, diagnosis being supported by biopsy. Xanthotoxin should be administered only in conjunction with a schedule of controlled doses of long-wave UV radiation. It is also used with long-wave UV radiation for repigmentation of idiopathic vitiligo (*29*). While a review of all the clinical studies is beyond the scope of this monograph, some of the more recent data are presented below.

A comparative trial involving 34 patients with plaque psoriasis assessed the efficacy of xanthotoxin administered by two different routes in combination with exposure to UV-A light. Each group of 17 patients was treated with the drug delivered either orally or in bath-water. Both treatments were effective; however, bath treatments were as effective or more effective than oral treatment and required less than half the dose of UV-A radiation required in the oral treatment group. Bath treatments also caused fewer side-effects (*26*).

A randomized, double-blind, right-left comparison trial investigated the efficacy of a combination of xanthotoxin plus UV-A radiation with topical calcipotriol in the treatment of vitiligo. Nineteen patients with bilateral symmetrical lesions were treated with an oral dose of 0.6 mg/kg bw of xanthotoxin 2 hours before exposure to sunlight three times per week. The patients were instructed to apply calcipotriol ointment at 50 µg/g on one side of the body and placebo ointment on the other. At the end of 6 months, 70% of patients showed significant improvement on the calcipotriol-treated side as compared with 35% on the placebo-treated

side ($P < 0.05$). It was concluded that the combination of xanthotoxin and calcipotriol is highly effective for the photochemotherapy of vitiligo (*25*).

A randomized comparison trial assessed the efficacy of xanthotoxin plus exposure to either UV-A or UV-B radiation for the treatment of plaque psoriasis in 100 patients. Both treatments were effective in reducing the number of plaques; no significant difference between the treatments was observed (*24*).

The efficacy of two UV-A radiation dosage regimens for treatment with oral administration of 0.6 mg/kg bw of xanthotoxin plus UV-A photochemotherapy for moderate–severe chronic plaque psoriasis was assessed using a half-body comparison. The high- and low-dose UV-A treatments were administered twice per week and symmetrical plaques were scored to determine the rate of resolution for each treatment. Patients were reviewed monthly for 1 year and 33 patients completed the study. Both regimens were effective and well tolerated; 42% of patients were clear 1 year after treatment and, for those whose psoriasis had recurred, there was no significant difference between the regimens in the number of days of remission (*23*).

In a clinical trial without controls, the efficacy of xanthotoxin in 10-mg capsules was assessed for the treatment of psoriasis, vitiligo and tinea versicolor (*43*). Fifty-three patients were treated orally with 0.25 mg/kg bw of xanthotoxin and then exposed to UV-A light for varying periods of time. In 87% of psoriasis patients, remission occurred after 30 treatments with xanthotoxin and UV-A, 85% of patients with vitiligo had acceptable repigmentation after 70 treatments, and 100% of patients with hypopigmentation tinea versicolor showed complete repigmentation after 12 treatments (*43*).

Exposure to Fructus Ammi Majoris or xanthotoxin in combination with exposure to UV-A light elicits a cutaneous inflammation, including erythema, oedema and bullae. The inflammatory processes culminate after 72 hours and hyperpigmentation appears after 1–2 weeks, lasting for several months. The mechanism of repigmentation is still a matter of debate. Affected cells may include keratinocytes, Langerhans cells and melanocytes in the epidermis as well as mononuclear and endothelial cells in the upper dermis. Epidermal changes include dyskeratosis, mild spongiosis and intracellular oedema at 24 hours, increasing at 72 hours. After 72 hours there is an increased mitotic activity in melanocytes and an increased number of functional melanocytes, with rises in the production of melanosomes and tyrosinase activity (*45*). Hyperpigmentation is due to the increased number of melanin granules in the epidermis, both in the Malpighian stratum and in the hyperkeratotic stratum corneum (*46, 47*).

Adverse reactions

One case of phototoxic dermatitis was reported in a patient with vitiligo after ingestion of Fructus Ammi Majoris (*48*). One case of allergic rhinitis and contact urticaria due to exposure to the fruits was reported (*49*). Phototoxic reactions were reported in subjects who handled the fruits and were subsequently exposed to sunlight. Erythema developed within 48–72 hours and persisted for several days. Skin that had been protected from sunlight for 30 days after exposure still had many erythematous areas and became irritated again when re-exposed to the sun. Small areas of darker pigmentation developed in the skin of some subjects (*35*). Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache, allergic symptoms and sleeplessness (*50*).

Photochemotherapy combining administration or application of xanthotoxin with UV-light treatment can be repeated many times (four times a week), and after about 14 days of therapy, a clear dilution of the epidermis results, cornification normalizes and the inflammation fades away. However, overdosage may result in severe erythema and blistering. This can partly be prevented through the application of β-carotene (*51*).

A 5-year prospective study of ophthalmological findings in 1299 patients treated with oral xanthotoxin plus UV photochemotherapy for psoriasis failed to demonstrate a significant dose-dependent increase in the risk of developing cataracts (*52*).

Other adverse reactions reported after treatment with xanthotoxin include itching, nausea, oedema, hypotension, nervousness, vertigo, depression, painful blistering, burning and peeling of the skin, pruritus, freckling, hypopigmentation, rash, cheilitis and erythema (*29*).

Contraindications

Fructus Ammi Majoris is contraindicated in diseases associated with photosensitivity, cataract, invasive squamous-cell cancer, known sensitivity to xanthotoxin (psoralens), and in children under the age of 12 years (*29*). The fruits are also contraindicated in pregnancy, nursing, tuberculosis, liver and kidney diseases, human immunodeficiency virus (HIV) infections and other autoimmune diseases (*22*).

Warnings

Care should be taken where there is a familial history of sunlight allergy or chronic infections; lotions should be applied only under direct supervision of a physician and should not be dispensed to the patient; for use only if response to other forms of therapy is inadequate. Serious burns

may result from exposure to UV-A light or sunlight, even through glass, if the correct dose and exposure schedule is not maintained.

If burning, blistering or intractable pruritus occurs, discontinue therapy until side-effects subside. Do not sunbathe for at least 24 hours prior to therapy and 48 hours after. Avoid direct and indirect sunlight for up to 8 hours after oral and 12–48 hours after topical treatment. If sunlight cannot be avoided, protective clothing and/or sunscreen must be worn. Following oral therapy, sunglasses must be worn for 24 hours. Avoid the ingestion of foods that contain furanocoumarins, such as limes, figs, parsley, celery, cloves, lemons, mustard and carrots (*29*).

Precautions

Drug interactions

The toxicity of Fructus Ammi Majoris may be increased when the fruits are administered with other photosensitizing agents such as coal tar, dithranol, griseofulvin, nalidixic acid, phenothiazines, sulfanilamides, tetracyclines and thiazides (*22, 29*).

Carcinogenesis, mutagenesis, impairment of fertility

A 95% ethanol extract of Fructus Ammi Majoris, 10.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102. Furthermore, an infusion of the fruits (concentration not specified) had antimutagenic effects against ethyl methanesulfonate- or 2-amino-anthracene-induced mutagenicity in *S. typhimurium* strains TA98 and TA100 (*53*).

A study of 4799 Swedish patients who received xanthotoxin/UV-A photochemotherapy in the period 1974–1985 showed a dose-dependent increase in the risk of squamous-cell cancer of the skin. Male patients who had received more than 200 treatments had over 30 times the incidence of squamous-cell cancer compared with the general population. Increases in the incidence of respiratory cancer, pancreatic cancer and colon cancer were also found (*54*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions
No information available on general precautions or precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms
Powdered dried fruits for oral use (*1*). Store in a tightly sealed container away from heat and light.

Posology
(Unless otherwise indicated)
Average daily dose: Fructus Ammi Majoris 0.02–0.04 g orally in divided doses (dosage schedule not specified) (*1*); xanthotoxin 0.25–0.7 mg/kg bw (*18, 20, 43*). Clinical treatment requires management by a health-care provider.

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Fructus Ammi Visnagae

Definition
Fructus Ammi Visnagae consists of the dried ripe fruits of *Ammi visnaga* (L.) Lam. (Apiaceae) (*1–3*).

Synonyms
Daucus visnaga L., *Selinum visnaga* E.H.L. Krause, *Sium visnaga* Stokes, *Visnaga daucoides* Gaertn. (*2, 4*). Apiaceae are also known as Umbelliferae.

Selected vernacular names
Ammi, besnika, bisagna, bishop's weed, herbe aux cure-dents, herbe aux gencives, kella, kella balady, khelâl dandâne, khella, nunha, owoc keli, Spanish carrot, viznaga, Zahnstocherkraut (*2, 5–8*).

Geographical distribution
Indigenous to the Mediterranean region. Cultivated in North America and in Argentina, Chile, Egypt, India, Islamic Republic of Iran, Mexico, Tunisia and Russian Federation (*2, 5–7*).

Description
An annual or biennial herb, up to 1.0 m high. Leaves dentate, in strips. Stems erect, highly branched. Inflorescence umbellate; rays, highly swollen at the base, become woody and are used as toothpicks. Fruits as described below (*2, 6*).

Plant material of interest: dried ripe fruits

General appearance
Cremocarp usually separated into its mericarps; rarely, occurs entire with a part of the pedicel attached. Mericarp small, ovoid, about 2 mm long, 1 m wide, brownish to greenish-brown, with a violet tinge. Externally glabrous, marked with five distinct, pale brownish, broad primary ridges, four inconspicuous, dark secondary ridges, and a disc-like stylopod at the apex. Internally comprises a pericarp with six vittae, four in the dorsal and two in the

commissural side, a large oily orthospermous endosperm and a small apical embryo. Carpophore single, passing into the raphe of each mericarp (*1, 2*).

Organoleptic properties
Odour: slightly aromatic; taste: aromatic, bitter, slightly pungent (*1, 2*).

Microscopic characteristics
Epidermis of the pericarp consists of polygonal cells, elongated on the ridges, with occasional crystals of calcium oxalate and finely striated cuticle, but no hairs. Mesocarp consists of parenchyma, traversed longitudinally by large, schizogenous vittae, each surrounded by large, slightly-radiating cells, and in the ridges by vascular bundles, each forming a crescent around a comparatively large lacuna and accompanied by fibres and reticulate, lignified cells. Innermost layer consists of large, polygonal, brown-walled cells, with thick, porous inner walls. Endocarp composed of narrow tangentially elongated cells, some of which are in regular arrangements in variously oriented groups, adhering to the brown seed coat, which is formed of similar but wider, shorter cells. Endosperm consists of polygonal, thick-walled, cellulosic parenchyma containing fixed oil and numerous small, oval aleurone grains, each enclosing a minute, rounded globoid and a microrosette crystal of calcium oxalate. Carpophore, passing at the apex into the raphe of each mericarp, traversed by a vascular bundle of fibres and spiral vessels (*1, 2*).

Powdered plant material
Brown and characterized by fragments of pericarp with some brownish pieces of vittae, reticulate cells, vessels and fibres. Also present are fragments with inner porous mesocarp cells crossed by and intimately mixed with variously oriented groups of endocarpal cells; and numerous fragments of endosperm. Other fragments show cells of the brown seed coat and aleurone grains 4–10 µm in diameter, containing microrosette crystals of calcium oxalate 2–5 µm in diameter. Hairs and starch grains absent (*1, 2*).

General identity tests
Macroscopic and microscopic examinations, microchemical tests (*1–3*), and thin-layer chromatography for the presence of khellin and visnagin (*3, 6, 9*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter
Not more than 2% (*3*).

Total ash
Not more than 8% (*2*).

Acid-insoluble ash
Not more than 3.5% (*1*).

Loss on drying
Not more than 10% (*3*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

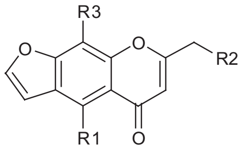
Chemical assays

Contains not less than 1% γ-pyrones (furanochromone derivatives) calculated as khellin, determined by spectrophotometry (*1–3*). A number of high-performance liquid chromatography methods are also available for quantitative analysis (*13–17*).

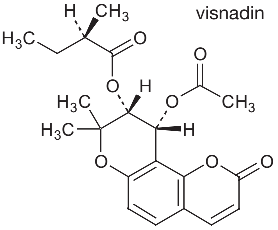
Major chemical constituents

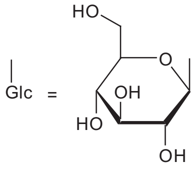
The major constituents are γ-pyrones (furanochromone derivatives; up to 4%), the principal compounds being khellin (0.3–1.2%) and visnagin (0.05–0.30%). Other γ-pyrones of significance are khellinol, ammiol, khellol and its glucoside khellinin (0.3–1.0%). A second group of major constituents are the coumarins (0.2–0.5%), the main one being the

pyranocoumarin visnadin (0.3%). Essential oil contains camphor, α-terpineol and linalool, among others, and also fixed oil (up to 18%) (*6, 8, 13–15, 18, 19*). Representative structures are presented below.



	R1	R2	R3
ammiol	OCH_3	OH	OCH_3
khellin	OCH_3	H	OCH_3
khellinin	OCH_3	O-Glc	H
khellinol	OH	H	OCH_3
khellol	OCH_3	OH	H
visnagin	OCH_3	H	H





β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

As an antispasmodic, muscle relaxant and vasodilator (*1*).

Uses described in traditional medicine

Treatment of mild anginal symptoms. Supportive treatment of mild obstruction of the respiratory tract in asthma, bronchial asthma or spastic bronchitis, and postoperative treatment of conditions associated with the presence of urinary calculi. Treatment of gastrointestinal cramps and painful menstruation (*6*). Internally as an emmenagogue to regulate menstruation, as a diuretic, and for treatment of vertigo, diabetes and kidney stones (*8*).

Pharmacology

Experimental pharmacology

Antimicrobial activities

A 50% acetone, 50% aqueous or 95% ethanol extract of Fructus Ammi Visnagae inhibited the growth of the fungus *Neurospora crassa* in vitro

(*20*). A 95% ethanol extract of the fruits inhibited the growth of *Mycobacterium tuberculosis* H37RVTMC 102 at a dilution of 1:40 in vitro (*21*). An aqueous extract of the fruits, 2–10 mg/ml inhibited growth and aflatoxin production by *Aspergillus flavus*; the effects were dose-dependent (*22*).

Antispasmodic effects

A methanol extract of the fruits, 1.0 mg/ml, inhibited potassium chloride-induced contractions in rabbit aorta in vitro (*23*). A chloroform extract of the fruits (concentration not specified) inhibited potassium chloride-induced contractions in guinea-pig aorta in vitro (*24*). Visnadin inhibited carbaminoylcholine- and atropine-induced contractions in isolated guinea-pig ileum at concentrations of 8.8 µmol/l and 0.02 µmol/l, respectively (*25*). Visnagin, 1.0 µmol/l, inhibited the contractile responses in rat aortic rings induced by potassium chloride, norepinephrine and phorbol 12-myristate 13-acetate, and spontaneous myogenic contractions of rat portal veins. Visnagin appears to inhibit only contractions mediated by calcium entry through pathways with low sensitivity to classical calcium channel blockers (*26, 27*).

Cardiovascular effects

Visnadin, 60.0 µg/ml or 120.0 µg/ml, increased coronary blood flow in isolated guinea-pig hearts by 46% and 57% and blood flow in a Laewan-Trendelenburg frog vascular preparation by 78% and 147%, respectively (*25*). Interarterial administration of 10.0 mg/kg body weight (bw) of visnadin to anaesthetized dogs increased blood flow by 30–100%, the effect lasting for 20 minutes after administration (*25*). Six compounds isolated from the fruits were tested for their ability to dilate coronary blood vessels in rabbits. Coronary vasospasm and myocardial ischaemia were induced by daily intramuscular injections of vasopressin tannate. All compounds were administered at 4.7 mg/kg bw per day by intramuscular injection for 7 days. Visnadin, dihydrosamidin, khellin and samidin effectively normalized the electrocardiogram, while visnagin and khellol glucoside were inactive (*28*). Positive inotropic effects were observed in dogs treated with intramuscular injections of samidin and khellol glucoside. No effects were observed for visnadin, dihydrosamidin, khellin and visnagin at varying doses (*28*).

Toxicology

In mice, the oral and subcutaneous median lethal doses (LD_{50}) of the fruits were 2.24 g/kg bw and > 370.0 mg/kg bw, respectively (*25*). In rats, the oral LD_{50} was > 4.0 g/kg bw, and in rabbits, the intravenous LD_{50} was

50.0 mg/kg bw. In dogs, the oral and intravenous LD_{50} values were 20.0 mg/kg bw and 200.0 mg/kg bw, respectively.

Subchronic oral administration of visnadin to mice, rats and rabbits at doses of up to 2.2 g/kg bw, up to 600.0 mg/kg bw and 6.0 mg/kg bw, respectively, produced no pronounced toxicity (*25*). In dogs, daily intramuscular injections of isolated chemical constituents of the fruits at ten times the therapeutic concentration for 90 days produced toxic effects characterized by increases in the serum glutamic-pyruvic and glutamic-oxaloacetic transaminases, increases in plasma urea, haematological changes and, in some cases, death. Of the six compounds tested, samidin was the most toxic, dihydrosamidin was the least toxic and khellin, visnagin, visnadin and khellol glucoside were of intermediate toxicity (*29*). The acute toxicities of khellin, visnagin, visnadin and samidin were assessed in mice and rats after intramuscular injection of doses of 0.316–3.16 mg/kg bw. The LD_{50} values were: khellin, 83.0 mg/kg bw in mice and 309.0 mg/kg bw in rats; visnagin, 123.0 mg/kg bw and 831.0 mg/kg bw; visnadin, 831.8 mg/kg bw and 1.213 g/kg bw; and samidin, 467.7 mg/kg bw and 1.469 g/kg bw (*30*).

Administration of *Ammi visnaga* seeds at 1.25–3% in the diet for 14 days had no toxic effects on turkeys or ducks. However, in chickens, the 3% dose produced mild signs of photosensitization within 6–8 days (*31*). Administration of 2.0 g/day for 4–8 days to goslings at age 3–5 weeks induced photosensitivity in the form of erythema, haematomas and blisters on the upper side of the beak (*32*).

The chemical constituents responsible for the induction of contact dermatitis in the mouse-ear assay were khellol, visnagin and khellinol, median irritant doses 0.125 µg/5 µl, 1.02 µg/5 µl and 0.772 µg/5 µl, respectively (*33*).

Clinical pharmacology

A placebo-controlled study assessed the effects of oral administration of 50 mg of khellin four times per day for 4 weeks on the plasma lipids of 20 non-obese, normolipaemic male subjects. Plasma lipids were measured every week during treatment and 1 week after cessation. Plasma total cholesterol and triglyceride concentrations remained unchanged, while high-density-lipoprotein cholesterol concentrations were significantly elevated, the effect lasting until 1 week after cessation of treatment (*34*).

Adverse reactions

Pseudoallergic reactions and reversible cholestatic jaundice have been reported (*35*). High oral doses of khellin (100.0 mg/day) reversibly elevated

the activities of liver transaminases and γ-glutamyltransferase (*35*). Prolonged use or overdose may cause nausea, vertigo, constipation, lack of appetite, headache and sleeplessness (*6*).

Contraindications

Fructus Ammi Visnagae is used in traditional systems of medicine as an emmenagogue (*8*), and its safety during pregnancy has not been established. Therefore, in accordance with standard medical practice, the fruits should not be used during pregnancy.

Warnings

No information available.

Precautions

General

Exposure to sun or other sources of ultraviolet light should be avoided during treatment because khellin causes photosensitivity (*35*).

Drug interactions

No drug interactions have been reported. However, khellin is reported to inhibit microsomal cytochrome P450 subenzymes, and may therefore decrease the serum concentrations of drugs metabolized via this pathway, such as ciclosporin, warfarin, estrogens and protease inhibitors (*36*).

Carcinogenesis, mutagenesis, impairment of fertility

A 95% ethanol extract of Fructus Ammi Visnagae, 10.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102. Furthermore, an infusion of the fruits had antimutagenic effects against ethyl methanesulfonate- or 2-amino-anthracene-induced mutagenicity in *S. typhimurium* strains TA98 and TA100 (*37*). Khellin also inhibited the mutagenicity of promutagens such as benzopyrene, 2-aminofluorene and 2-aminoanthracene in *S. typhimurium* TA98. However, there was no effect on direct-acting mutagens, such as 2-nitrofluorene, 4-nitro-*o*-phenylenediamine, in *S. typhimurium* TA100 (*36*).

Pregnancy: teratogenic effects

Intragastric administration of up to 600.0 mg/kg bw of visnadin to rats on days 8–12 of pregnancy produced no toxic effects (*25*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers
Owing to the lack of safety data, Fructus Ammi Visnagae should be taken internally only under the supervision of a health-care provider.

Paediatric use
Owing to the lack of safety data, Fructus Ammi Visnagae should be taken internally only under the supervision of a health-care provider.

Other precautions
No information available on precautions concerning drug and laboratory test interactions.

Dosage forms
Dried fruits, infusions, extracts and other galenical preparations (*35*). Store fully dried fruits in well closed containers in a cool and dry place protected from light (*1*).

Posology
(Unless otherwise indicated)
Average daily dose: Fructus Ammi Visnaga 0.05–0.15 g (*1*).

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Fructus Anethi

Definition

Fructus Anethi consists of the dried ripe fruits of *Anethum graveolens* L. (Apiaceae) (*1, 2*).

Synonyms

Pastinaca anethum Spreng., *Peucedanum graveolens* Benth. & Hook., *Selinum anethum* Roth (*1, 3*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Aneth, anethum, bo-baluntshep, dill, Dill-Fenchel, eneldo, faux anis aneth, fenouil bâtard, fenouil puant, garden dill, Gartendill, hinan, inondo, jirashi, kapor, kerwiya amya, koper, sadapa, sadhab el barr, satakuppa, satakuppi, sathukuppa, satpushpa, shabat, shabath, shatapuspi, shebet, shebid, sheved, shevid, shi ra ja, shibth, sibt, slulpha, soolpha, sova, sowa, s-sebt, suva, sulpha, sutopsha, thian ta takkataen, zira (*1, 4–9*).

Geographical distribution

Indigenous to southern Europe. Cultivated widely throughout the world (*1, 4, 5, 8, 10, 11*).

Description

An aromatic annual or biennial herb, 40–120 cm high, with an erect hollow green stem, branching above. Leaves glaucous, tripinnate, with linear leaflets. Inflorescence umbellate with 15–30 rays; bracts and bracteoles absent; flowers yellow. Fruits deep brown, flattened, oval, with protruding clear back ribs with sharp edges (*1, 5, 11–13*).

Plant material of interest: dried ripe fruits

General appearance

Mericarps separate, broadly oval, chocolate-brown, each dorsally compressed, 3–4 mm long, 2–3 mm wide and 1 mm thick, the ratio of length

to width being approximately 1.6:1.0; two ventral ridges prolonged into wide yellowish membranous wings; three dorsal ridges, brown, inconspicuous. Transversely cut surface of the fruit surface shows six vittae, four in the dorsal and two in the commissural side; five vascular bundles, three in the ridges and two in the wings, those in the wings being wider than those in the ridges (*1, 4, 5*).

Organoleptic properties

Odour: characteristic, aromatic; taste: characteristic, pleasant (*1, 4, 5*).

Microscopic characteristics

Mericarp has four vittae in the dorsal and two in the commissural side. Outer epidermis has a striated cuticle. Mesocarp contains lignified, reticulate parenchyma. Inner epidermis composed of tabular cells frequently with wavy walls, tabular cells all parallel (e.g. parquet arrangement). Thick-walled parenchyma of the endosperm contains fixed oil, aleurone grains and microrosette crystals of calcium oxalate (*1, 4, 14, 15*).

Powdered plant material

Greyish-brown powder characterized by fragments of pericarp with a few brownish pieces of vittae. Outer epidermis has striated cuticle. Mesocarp fragments show lignified reticulate parenchyma, inner epidermis, tabular cells frequently wavy walled, numerous fragments of endosperm; aleurone grains, fixed oil and microrosette crystals of calcium oxalate (*1*).

General identity tests

Macroscopic and microscopic examinations (*1, 2*), and thin-layer chromatography (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Chemical

Not less than 3.0% essential oil (*2*).

Foreign organic matter

Not more than 2.0% (*1*).

Total ash
Not more than 11.0% (*1*).

Acid-insoluble ash
Not more than 1.5% (*2*).

Water-soluble extractive
Not less than 15.0% (*2*).

Alcohol-soluble extractive
Not less than 4.0% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

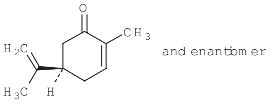
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

Other purity tests
Loss on drying test to be established in accordance with national requirements.

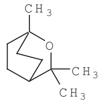
Chemical assays
Contains not less than 2.0% essential oil (*1*). Gas chromatography (*19*) and gas chromatography–mass spectrometry (*20*) methods for essential oil constituents are also available.

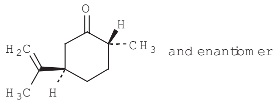
Major chemical constituents
Contains 2–5% essential oil, the major constituent of which is carvone (20–60%) (*11, 21, 22*). The carvone content in plants cultivated in India is reported to be 6% less than in those cultivated in Europe (*9*). Other characteristic terpenoid essential oil constituents include dihydrocarvone, 1,8-cineole, *p*-cymene, limonene, α-phellandrene, α-pinene and α-terpinene. The flavonoids present include kaempferol-glucuronide (*22, 23*).

Dillapiol is found in the essential oil obtained from plants cultivated in Egypt, India and Japan (*24*). Representative structures are presented below.

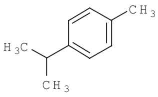


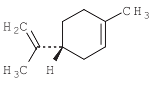
carvone

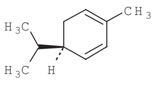

1,8-cineole

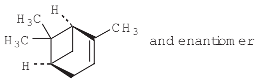


dihydrocarvone

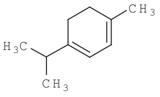

p-cymene


(+)-limonene


(-)-α-phellandrene



α-pinene


α-terpinene

Medicinal uses

Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Treatment of dyspepsia (*25*), gastritis and flatulence (*1, 26*), and stomach ache (*27*).

Uses described in traditional medicine
As an aphrodisiac, analgesic, antipyretic, diuretic, emmenagogue, galactagogue, appetite stimulant and vaginal contraceptive. Treatment of diarrhoea, asthma, neuralgia, dysuria, dysmenorrhoea, gallbladder disease, insomnia, hiatus hernia and kidney stones (*9, 26–29*).

Pharmacology

Experimental pharmacology

Antispasmodic and carminative activities
A 50% ethanol extract of Fructus Anethi inhibited acetylcholine- and histamine-induced contractions of guinea-pig ileum in vitro (*30*). The essential oil, 50 mg/ml, reduced contractions of rabbit intestine (*31*). The essential oil (containing the monoterpenes and phenylpropanes: dillapiol, myristicin and isomyristicin) (concentration not specified) acted as a mild carminative and stomachic (*32*). The essential oil had carminative activity and reduced foaming in vitro, median effective concentration 2.0% (*33*).

Anti-inflammatory and analgesic activities
A single topical application of an ethanol extract of the fruits, at a dose corresponding to 1.0 mg/20 µl of a 10.0-mg dried methanol extract dissolved in 200.0 µl of ethanol, to the inner and outer surface of the ear of

mice inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13 acetate by 60% (*34*). Ethyl acetate and hexane extracts of the fruits (concentration not specified) were inactive in this assay. A 10% aqueous extract of the fruits and a 5% aqueous solution of the essential oil had analgesic effects in mice as assessed in the hot plate and acetic acid writhing tests. The action of the fruits at 1.0 g/kg body weight (bw) was comparable with that of acetylsalicyclic acid at 200.0 mg/kg bw (*35*).

Miscellaneous effects

Intravenous administration of 12.5 mg/kg bw of a 70% dried ethanol extract of the fruits, dissolved in normal saline, to dogs had a diuretic effect, with a 2.2-fold increase in urine output. Intravenous administration of 25.0 mg/kg bw of a 70% ethanol extract to dogs reduced blood pressure. Intravenous administration of 4.0 µl/kg bw of the essential oil induced diuresis in dogs lasting 80 minutes, with increased sodium and calcium ion excretion (*36*). Intravenous administration of 5.0–10.0 mg/kg bw of a 5% seed oil in saline to cats increased respiration volume and lowered blood pressure; intraperitoneal administration of 35.0 mg/kg bw of the seed oil to guinea-pigs induced anaphylactic shock (*11*). A single intragastric dose of 250.0 mg/kg bw of a 50% ethanol extract of the fruits to fasted rats reduced blood glucose levels by 30% compared with controls (*30*).

Toxicology

In a report by a national regulatory authority "generally regarded as safe status" was granted to Fructus Anethi as a flavouring agent in 1976 (*37*).

Clinical pharmacology

No information available.

Adverse reactions

Allergic reactions to Fructus Anethi including oral pruritus, tongue and throat swelling and urticaria, as well as vomiting and diarrhoea were reported in one patient with a history of allergic rhinitis (*38*).

Contraindications

Traditionally, extracts of fruits (seeds) have been used as a contraceptive and to induce labour (*4*). Furthermore, extracts of the fruits may have teratogenic effects (*39*). Therefore, the use of Fructus Anethi during pregnancy and nursing is not recommended.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A chloroform–methanol (2:1) extract of the fruits was not mutagenic in concentrations up to 100.0 mg/plate in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, with or without metabolic activation. A 95% ethanol extract was also without mutagenic activity in the same test system (*40*).

An essential oil prepared from the fruits was cytotoxic to human lymphocytes in vitro, and was active in the chromosome aberration and sister chromatid exchange tests in the same system. The oil was inactive in the *Drosophila melanogaster* somatic mutation and recombination test in vivo (*41*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic effects during pregnancy; or paediatric use.

Dosage forms

Dried fruits for teas, essential oil and other galenical preparations for internal applications. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average daily dose: Fructus Anethi 3 g; essential oil 0.1–0.3 g; or equivalent for other preparations (*25*).

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Aetheroleum Anisi

Definition

Aetheroleum Anisi consists of the essential oil obtained by steam distillation from the dry ripe fruits of *Pimpinella anisum* L. (Apiaceae) (*1–5*).[1]

Synonyms

Anisum officinarum Moench, *A. vulgare* Gaertn., *Apium anisum* (L.) Crantz, *Carum anisum* (L.) Baill., *Pimpinella anisum cultum* Alef., *P. aromatica* Bieb., *Selinum anisum* (L.) E.H.L. Krause, *Sison anisum* Spreng., *Tragium anisum* Link (*1, 6–8*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Anacio, Änes, Aneis, anice, anice verde, Anis, anisbibernelle, anis verde, anis vert, anise, anisoon, anisum, ánizs, anizsolaj, annsella, badian, badian rumi, boucage, boucage anis, Grüner Anis, habbat hlawa, jintan manis, jinten manis, petit anis, pimpinelle, razianag, razianaj, roomy, saunf, sweet cumin, yansoon (*1, 6–10*).

Geographical distribution

Indigenous to the eastern Mediterranean region, western Asia and Europe. Cultivated in southern Europe and northern Africa, and in Argentina, Bulgaria, Chile, China, India, Islamic Republic of Iran, Japan, Mexico, Romania, Russian Federation and Turkey (*8*).

Description

An aromatic annual herb, up to 60 cm high with an erect, cylindrical, striated, smooth stem. Leaves alternate below, opposite above, the lower being long-petioled, ovate–orbicular, dentate, the upper with short dilated petioles, pinnatifid or ternately pinnate with long, entire or cut cuneate segments. Inflorescence long-stalked, compound umbel with 8–14 rays; flowers small, white, each on a long hairy pedicel. Fruit comprises a

[1] The *European pharmacopoeia (5)* permits the inclusion of the essential oil of *Illicium verum Hook.*

mouse-shaped cremocarp with a small stylopod and two minutely pubescent mericarps that do not readily separate from the carpophore (*6, 11*).

Plant material of interest: essential oil

General appearance

A clear, colourless or pale yellow liquid, solidifying on cooling, practically insoluble in water, miscible with alcohol, ether, light petroleum or methylene chloride (*1, 5*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet, strongly aromatic (*1*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Thin-layer chromatography for the presence of anethole, anisaldehyde and linalool. A gas chromatography method is also available (*5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Chemical

Soluble in three parts ethanol (90%) at 20 °C (*4*). Relative density 0.978–0.994 (*5*). Refractive index 1.552–1.561 (*5*). Freezing-point 15–19 °C (*5*). Acid value not more than 1.0 (*5*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*5*). For other pesticides, see the *European pharmacopoeia* (*5*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*13*).

Heavy metals

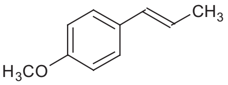
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

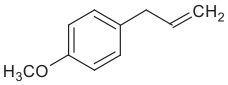
Other purity tests
Tests for foreign organic matter, total ash, acid-insoluble ash, water-soluble extractive, alcohol-soluble extractive and loss on drying not applicable.

Chemical assays
Contains 0.1–1.5% linalool, 0.5–6.0% methylchavicol, 0.1–1.5% α-terpineol, < 0.5% *cis*-anethole, 84–93% *trans*-anethole, 0.1–3.5% *p*-anisaldehyde (*5*).

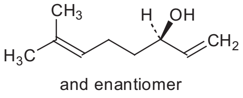
Major chemical constituents
The major constituents are *trans*-anethole (84–93%), *cis*-anethole (< 0.5%), methylchavicol (estragole, isoanethole; 0.5–6.0%), linalool (0.1–1.5%) and *p*-anisaldehyde (0.1–3.5%) (*5*). The structures of *trans*-anethole, methylchavicol, β-linalool and *p*-anisaldehyde are presented below.



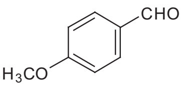
trans-anethole



methylchavicol



β-linalool



p-anisaldehyde

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Treatment of dyspepsia and mild inflammation of the respiratory tract (*14, 15*).

Uses described in traditional medicine
As an aphrodisiac, carminative, emmenagogue, galactagogue and insecticide. Treatment of chronic bronchitis (*8, 10*).

Pharmacology
Experimental pharmacology
Antimicrobial activity

Aetheroleum Anisi, 500 mg/l, inhibited the growth of *Alternaria alternata, Alternaria tenuissima*, *Aspergillus* spp., *Botryodiplodia* spp., *Clado-*

sporium herbarum, Cladosporium werneckii, Colletotrichum capsici, Curvularia lunata, Curvularia pallescens, Fusarium moniliforme, F. oxysporum, Mucor spinescens, Penicillium chrysogenum, P. citrinum and *Rhizopus nigricans* (*16*). The oil (concentration not specified) inhibited the growth of *Aspergillus flavus, A. niger, Fusarium oxysporum* and *Penicillium* spp. in vitro (*17*). The oil, 1.0 ml/plate, inhibited the growth of *Rhizoctonia solani* and *Sclerotinia sclerotiorum*, but was inactive against *Fusarium moniliforme* and *Phytophthora capsici* in vitro (*18*). The oil (concentration not specified) did not inhibit the growth of *Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa* or *Staphylococcus aureus* but did inhibit that of *Aspergillus aegyptiacus, Penicillium cyclopium* and *Trichoderma viride* in vitro (*19*). The oil (concentration not specified) was active against *Bacillus subtilis, Escherichia coli, Lentinus lepideus, Pseudomonas aeruginosa* and *Staphylococcus aureus* (*20*). The oil inhibited the growth of *Candida albicans, Candida krusei, Candida parapsilosis, Candida tropicalis, Microsporum gypseum, Rhodotorula rubra* and *Saccharomyces cerevisiae*, minimum inhibitory concentration (MIC) 0.097%, and *Geotrichum* spp., MIC 1.562% (*21*).

Anticonvulsant activity

Intraperitoneal administration of 1.0 ml/kg body weight (bw) of the oil to mice suppressed tonic convulsions induced by pentylenetetrazole or maximal electroshock (*22*). Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents provided protection against convulsions induced by pentylenetetrazole, picrotoxin and electroshock (*23, 24*). Intraperitoneal administration of 2.5 g/kg bw of linalool to mice interfered with glutamate function and delayed convulsions induced by *N*-methyl-D-aspartate (*25*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes. The effects of linalool were investigated on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes. Linalool, 1.0 mmol/l, reduced potassium-stimulated glutamate release (*26*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

Anti-inflammatory activity

Anethole is a potent inhibitor of tumour necrosis factor (TNF)-induced nuclear factor (NF)-κβ activation, inhibitor-κβα phosphorylation and degradation, and NF-κβ reporter gene expression in vitro, demonstrating that anethole suppresses inflammation by inhibiting TNF-induced cellular responses (*27*).

Antispasmodic activity

The oil inhibited the phasic contractions of ileal myenteric plexus-longitudinal muscle preparations isolated from guinea-pigs in vitro, median effective dose 60 mg/l (*28*). The oil, 1:20 000, decreased the rate and extent of contractions in intestinal smooth muscle isolated from rats, cats or rabbits in vitro, and antagonized the stimulant activity of acetylcholine, barium chloride, pilocarpine and physostigmine (*29*). Anethole, 0.05–1.00 mg/ml, blocked twitching induced by acetylcholine and caffeine in toad rectus abdominis and sartorius muscles, but had no effect on skeletal muscle twitching induced by nerve stimulation in isolated rat diaphragm (*30*).

Bronchodilatory activity

The oil, 1.0 mmol/l, had relaxant effects in precontracted, isolated guinea-pig tracheal chains indicating a bronchodilatory effect. It also induced a parallel rightwards shift in the methacholine-response curve (methacholine is a muscarinic receptor antagonist), indicating that the bronchodilatory activity may be due to an inhibitory effect of the oil on the muscarinic receptors (*31*).

Estrogenic activity

Subcutaneous administration of 0.1 ml of the oil to ovariectomized rats had an estrogenic effect equivalent to that of 0.1 µg of estradiol (*32*). Intraperitoneal administration of 0.1 ml of the oil had a uterine relaxation effect in female rats (*32*). Anethole is thought to be the estrogenic component of the oil; polymers of this compound, such as dianethole and photoanethole, have also been suggested (*33*).

Expectorant activity

Intragastric administration of 10.0–50.0 mg/kg bw of the oil to guinea-pigs increased bronchial secretions, demonstrating an expectorant effect (*34*). Intragastric administration of two drops of the oil as an emulsion with gummi arabicum to cats induced hypersecretion of the respiratory tract (*35*). However, other researchers have demonstrated that administration of the oil to cats by steam inhalation had no effect on respiratory tract fluid except when given in toxic doses, which increased the output (*36*). Administration of the oil by inhalation to anaesthetized rabbits did not appreciably affect respiratory tract fluids until doses of 720.0 mg/kg bw and over were used in a vaporizer (*36, 37*). At this dose, 20% of the animals died and there was local irritation of the lining of the respiratory tract, which appeared as congestion at 6 hours and progressed to leukocytic infiltration and destruction of the ciliated mucosa at 24 hours (*36*). Inhalation of 1 ml/kg bw of anisaldehyde in anaesthetized rabbits signifi-

cantly increased ($P < 0.05$) the volume of respiratory fluid collected for 4–6 hours after treatment and decreased the specific gravity of the fluid in treated animals compared with untreated controls (*38*).

Liver effects

Subcutaneous administration of 100.0 mg/kg bw of the oil per day for 7 days stimulated liver regeneration in partially hepatectomized rats (*39*).

Toxicology

The oral median lethal dose (LD_{50}) of anisaldehyde in rats was 1.51 g/kg bw, with death occurring within 4–18 hours following depression of the central nervous system (*40*). The oral LD_{50} in guinea-pigs was 1.26 g/kg bw, death occurring after 1–3 days (*40*).

The safety and metabolism of *trans*-anethole were evaluated in rats as a model for assessing the potential for hepatotoxicity in humans exposed to the compound as a flavouring agent. In chronic dietary studies in rats, hepatotoxicity was observed when the estimated daily hepatic production of anethole epoxide exceeded 30 mg/kg bw. Chronic hepatotoxicity and a low incidence of liver tumours were observed at a dietary intake of *trans*-anethole of 550.0 mg/kg bw per day (*41*). The effects of *trans*-anethole on drug metabolizing enzymes were assessed in rats; intragastric administration of 125.0 mg/kg or 250.0 mg/kg bw per day for 10 days had no effect on total cyctochrome P450 content in liver microsomes (*42*). In a chronic feeding study, *trans*-anethole was administered to rats in the diet at concentrations of 0, 0.25%, 0.5% and 1.0% for 117–121 weeks, giving an average dose of 105–550.0 mg/kg bw per day. No abnormalities related to treatment were observed with the exception of a very low incidence of hepatocarcinomas in female animals treated with the 1.0% dose (*43*).

The acute oral LD_{50} of anethole in rats was 2090.0 mg/kg bw; repeated doses of 695.0 mg/kg bw caused mild liver lesions consisting of slight discoloration, mottling and blunting of the lobe edges (*33*).

Clinical pharmacology

The absorption of anethole from the gastrointestinal tract was assessed in healthy volunteers. The drug was rapidly absorbed from the gastrointestinal tract and rapidly eliminated in the urine (54–69%) and through the lungs (13–17%). The principal metabolite was 4-methoxyhippuric acid (approximately 56%); other metabolites were 4-methoxybenzoic acid and three other unidentified compounds (*44, 45*). Increases in drug dose did not alter the pattern of metabolite distribution in humans, contrary to findings in animal models (*46*).

Adverse reactions

Contact dermatitis was reported in a cake factory worker after external exposure to a 5% concentration of Aetheroleum Anisi (*47*). Occasional allergic reactions to the oil affecting the skin, respiratory tract and gastrointestinal tract are reported (*15*). Inhalation of powdered Fructus Anisi induced an allergic effect in one subject with asthma. Skin-prick tests showed a positive reaction to the fruits and the patient had high specific anti-aniseed immunoglobulin E antibodies in his blood (*48*). Anethole toxicity in infants has been reported, and presents clinically with symptoms of hypertonia, continued crying, atypical ocular movements, twitching, cyanosis, vomiting and lack of appetite (*7, 49*). Ingestion of 1.0–5.0 ml of the oil can result in nausea, vomiting, seizures and pulmonary oedema (*50*). In cases of overdose (> 50 mg/kg), the ingestion of milk and alcohol is contraindicated owing to increased resorption.

Contraindications

Aetheroleum Anisi is contraindicated in cases of known allergy to aniseed and anethole (*48*). Owing to the traditional use of the oil as an emmenagogue and to induce labour, its experimental estrogenic and potential mutagenic effects, and reports of anethole toxicity in infants (*7, 49*), use of the oil in pregnancy and nursing, and in children under the age of 12 years is contraindicated.

Warnings

Applications of Aetheroleum Anisi should be limited to inhalation therapy (*51*).

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

Inconsistent results have been reported concerning the mutagenicity of *trans*-anethole in the *Salmonella*/microsome assay. One group showed that anethole was mutagenic (*52*), another that it was very weakly mutagenic in *S. typhimurium* strains TA1535, TA100 and TA98 (*53*). In a further study, *trans*-anethole (concentrations not specified) did not increase the mutant frequency in the *Salmonella*/microsome assay, but did increase mutant frequency in the L5178Y mouse-lymphoma TK+/- assay in a dose-dependent manner, with metabolic activation (*49*). *Trans*-anethole did not induce chromosome aberrations in vitro in the Chinese hamster ovary cell assay (*49*). *Trans*-anethole was weakly hepatocarcinogenic in female rats when administered at a dose of 1% in the diet for 121 weeks;

however, this effect is not mediated by a genotoxic event (*54*). *Trans*-anethole was investigated for its antifertility activity in rats, after intragastric administration of doses of 50.0 mg/kg bw, 70.0 mg/kg bw and 80.0 mg/kg bw (*55*). Anti-implantation activity of 100% was observed in animals treated with the highest dose. The compound has been reported to show estrogenic, antiprogestational, androgenic and antiandrogenic activities (*55*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; and teratogenic effects in pregnancy.

Dosage forms
Essential oil. Preparations containing 5–10% essential oil for inhalation are also available. Store in a well-filled, tightly sealed container, protected from light and heat (*5*).

Posology
(Unless otherwise indicated)
Average daily dose for internal use: essential oil 0.3 g; equivalent for other preparations (*15*).

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Fructus Anisi

Definition

Fructus Anisi consists of the dried fruits of *Pimpinella anisum* L. (Apiaceae) (*1–3*).

Synonyms

Anisum officinarum Moench, *A. vulgare* Gaertn., *Apium anisum* (L.) Crantz, *Carum anisum* (L.) Baill., *Pimpinella anisum cultum* Alef., *P. aromatica* Bieb., *Selinum anisum* (L.) E.H.L. Krause, *Sison anisum* Spreng., *Tragium anisum* Link (*1, 2, 4, 5*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Anacio, Änes, Aneis, anice, anice verde, Anis, anisbibernelle, anis verde, anis vert, anise, anisoon, anisum, ánizs, anizsolaj, annsella, badian, badian rumi, boucage, boucage anis, Grüner Anis, habbat hlawa, jintan manis, jinten manis, petit anis, pimpinelle, razianag, razianaj, roomy saunf, sweet cumin, yansoon (*1, 2, 4–7*).

Geographical distribution

Indigenous to the eastern Mediterranean region, western Asia and Europe. Cultivated in southern Europe and northern Africa, and in Argentina, Bulgaria, Chile, China, India, Islamic Republic of Iran, Japan, Mexico, Romania, Russian Federation and Turkey (*5, 8*).

Description

An aromatic annual herb, up to 60 cm high, with an erect, cylindrical, striated, smooth stem. Leaves alternate below, opposite above, the lower being long-petioled, ovate–orbicular, dentate, the upper with short, dilated petioles, pinnatifid or ternately pinnate with long, entire or cut cuneate segments. Inflorescence long-stalked, compound umbel with 8–14 rays; flowers small, white, each on a long hairy pedicel. Fruit comprises a mouse-shaped cremocarp with a small stylopod and two minutely pubescent mericarps that do not readily separate from the carpophore (*2, 9*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp, partly separated into its mericarps, often entire, remaining attached to a slender pedicel 2–12 mm long; pear-shaped, 3–6 mm long and 2–3 mm wide, enlarged at the base and tapering at the apex, somewhat laterally compressed, crowned with a disc-like nectary; stylopod ends with the remains of two diverging styles; greyish or greenish-grey, seldom greyish-brown. Mericarp externally rough to the touch owing to the presence of numerous very short, stiff hairs; marked with five very slightly raised, filiform, pale-brown primary ridges; commissural surface, nearly flat, with two dark brownish, longitudinal areas, containing vittae, separated by a middle paler area; internally comprises a pericarp with numerous branched vittae in the dorsal side and usually only two large ones in the commissural side, a large white oily endosperm, not deeply grooved on the commissural side, and a small apical embryo. Carpophore forked, passing at the apex into the raphe of each pericarp (*1, 2*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet, strongly aromatic (*1, 2*).

Microscopic characteristics

Pericarp epidermis consists of cells with striated cuticle, many of which project into short, conical, curved, thick-walled, unicellular, sometimes bicellular, non-glandular hairs, with bluntly pointed apex and finely warty cuticles. Mesocarp formed of thin-walled parenchyma, traversed longitudinally by numerous schizogenous vittae, with brown epithelial cells and, in each primary ridge, by a small vascular bundle, accompanied by a few fibres; also a patch of porous or reticulate lignified cells in the middle of the commissural side, but not in the ridges. Endocarp composed of narrow, tangentially elongated, thin-walled cells, except when adjacent to the reticulate cells in the mesocarp, where it is formed of porous, lignified and reticulately thickened cells. Testa consists of one layer of tangentially elongated cells with yellowish-brown walls, closely adhering to the endocarp except along the commissural surface, where separated by a large cavity. Endosperm formed of polygonal thick-walled cellulosic cells containing fixed oil and many aleurone grains, each enclosing one globoid and one or two microrosette crystals of calcium oxalate with dark centres. Carpophore traversed by a vascular bundle of fibres and spiral vessels (*1, 2*).

Powdered plant material
Grey, greenish-brown or yellowish-brown, characterized by numerous, almost colourless fragments of endosperm; abundant minute oil globules; numerous warty simple hairs 25–100 µm long and 10–15 µm wide. Fragments of pericarp with yellowish-brown, comparatively narrow, branching vittae, usually crossed by the cells of the endocarp, the ratio of the width of these cells to that of the vittae varying from 1:7 to 1:5. Few fibres and very scanty pitted lignified parenchyma; aleurone grains 2–15 µm in diameter. Microrosette crystals of calcium oxalate 2–10 µm in diameter, each containing a minute air bubble (*1, 2*).

General identity tests
Macroscopic and microscopic examinations (*2, 3*), and thin-layer chromatography for the presence of anethole (*3*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter
Not more than 2.0% (*3*).

Total ash
Not more than 12.0% (*3*).

Acid-insoluble ash
Not more than 2.5% (*1, 3*).

Loss on drying
Not more than 7.0% (*3*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*3*). For other pesticides, see the *European pharmacopoeia* (*3*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*11*).

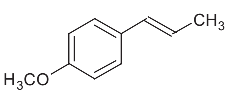
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

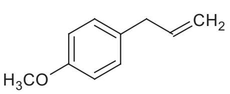
Other purity tests
Chemical, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 2% (v/w) essential oil (*3*). A high-performance liquid chromatography method for the analysis of phenylpropanoid constituents is available (*12*).

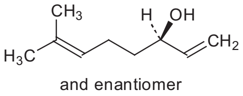
Major chemical constituents
Contains 1.5–5.0% essential oil, the major constituents of which are linalool (0.1–1.5%), methylchavicol (estragole, isoanethole; 0.5–6.0%), α-terpineol (0.1–1.5%), *cis*-anethole (< 0.5%), *trans*-anethole (84–93%), *p*-anisaldehyde (0.1–3.5%) (*3*). The structures of *trans*-anethole, methylchavicol, β-linalool and *p*-anisaldehyde are presented below.



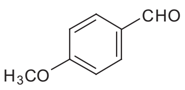
trans-anethole



methylchavicol



β-linalool



p-anisaldehyde

Medicinal uses
Uses supported by clinical data
No information available.

Uses described in pharmacopoeias and well established documents
Treatment of dyspepsia and mild inflammation of the respiratory tract (*13, 14*).

Uses described in traditional medicine
As an aphrodisiac, carminative, emmenagogue, galactagogue and tonic, and for treatment of asthma, bronchitis, diarrhoea, fever, spasmodic cough, flatulent colic and urinary tract infections (*5, 7, 15*).

Pharmacology
Experimental pharmacology
Analgesic and central nervous system activity
Intraperitoneal or intragastric administration of a dried ether extract of the fruits dissolved in normal saline did not potentiate barbiturate-

induced sleeping time when administered to mice in doses of up to 200.0 mg/kg body weight (bw) (*16*).

Antimicrobial activity

A 95% ethanol extract of the fruits, 50 µl/plate, inhibited the growth of *Staphylococcus aureus* in vitro (*17*). A dried methanol extract of the fruits inhibited the growth of *Helicobacter pylori* in vitro, minimum inhibitory concentration (MIC) 100.0 µg/ml (*18*). A decoction of the fruits did not inhibit the growth of *Aspergillus niger*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* or *Staphylococcus aureus* in vitro at concentrations of up to 62.5 mg/ml (*19*). An ethanol extract of the fruits inhibited the growth of *Candida albicans*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *Microsporum gypseum*, *Rhodotorula rubra* and *Saccharomyces cerevisiae*, MIC 0.097%, and *Geotrichum* spp., MIC 1.562% (*20*).

Anticonvulsant activity

Intraperitoneal administration of 4.0 mg/kg bw of a dried 95% ethanol extract of the fruits dissolved in normal saline to mice inhibited convulsions induced by supramaximal electroshock. At the same dose, the extract was ineffective against convulsions induced by pentylenetetrazole and strychnine (*21*).

Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents provided protection against convulsions induced by pentylenetetrazole, picrotoxin, and electroshock (*22*, *23*). Intraperitoneal administration of 2.5 g/kg bw of linalool to mice interfered with glutamate function and delayed *N*-methyl-D-aspartate-induced convulsions (*24*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes. The effects of linalool on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes were investigated. Linalool, 1.0 mmol/l, reduced potassium-stimulated glutamate release (*25*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

Anti-inflammatory activity

External application of 2.0 mg of a methanol extract of the fruits inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate in mice (*26*). External application of 20.0 µl of an ethyl acetate or hexane extract of the fruits did not inhibit ear inflammation induced by *O*-tetradecanoylphorbol-13-acetate in mice; application of 20.0 µl of a methanol extract was weakly active in the same assay (*27*). Anethole is a potent inhibitor of tumour necrosis factor (TNF)-induced nuclear factor (NF)-κβ activation, inhibitor-κβα phosphorylation and degradation, and

NF-κβ reporter gene expression in vitro, demonstrating that anethole suppresses inflammation by inhibiting TNF-induced cellular responses (*28*).

Bronchodilatory activity

The fruits, 1.0 mmol/l, had significant ($P < 0.05$) relaxant effects in precontracted, isolated guinea-pig tracheal chains in vitro, indicating a bronchodilatory effect. At the same dose, the fruits induced a parallel rightwards shift in the methacholine-response curve, indicating that the bronchodilatory activity may be due to an inhibitory effect on the muscarinic receptors (*29*).

Hypotensive activity

Intravenous administration of 50.0 mg/kg bw of a dried 50% ethanol extract of the fruits dissolved in normal saline to dogs decreased blood pressure (*30*). Intragastric administration of an aqueous extract of the fruits reduced atropine-induced hypertension at a dose of 10.0% (no further information available) (*31*). Administration of an unspecified extract of the fruits had a diuretic effect in rabbits, which was blocked by pretreatment with morphine (*32*).

Platelet aggregation inhibition

A methanol extract of the fruits, 500.0 µg/ml, inhibited collagen-induced platelet aggregation in human platelets (*33*).

Smooth muscle stimulant activity

An aqueous extract of the fruits, 10.0% in the bath medium, stimulated contractions of isolated frog rectus abdominis muscle and rat jejunum strips (*31*). Anethole, 0.05–1.00 mg/ml, blocked twitching induced by acetylcholine and caffeine in toad rectus abdominis and sartorius muscles, but had no effect on skeletal muscle twitching in isolated rat diaphragm induced by electrical nerve stimulation (*34*).

Toxicity

For intraperitoneal injection of a dried 50% ethanol extract of the fruits dissolved in normal saline in mice, the maximum tolerated dose was 500.0 mg/kg bw, median lethal dose (LD_{50}) 750.0 mg/kg (*30*).

The safety and metabolism of *trans*-anethole were evaluated in rats as a model for assessing the potential for hepatotoxicity in humans exposed to the compound as a flavouring agent. In chronic dietary studies in rats, hepatotoxicity was observed when the estimated daily hepatic production of anethole epoxide exceeded 30.0 mg/kg bw. Chronic hepatotoxicity and a low incidence of liver tumours were observed at a dietary intake of *trans*-anethole of 550.0 mg/kg bw per day (*35*). The effects of *trans*-anethole on

drug-metabolizing enzymes were assessed in rats; intragastric administration of 125.0 mg/kg bw or 250.0 mg/kg bw per day for 10 days had no effect on total cyctochrome P450 content in liver microsomes (*36*). In a chronic feeding study, *trans*-anethole was administered to rats in the diet at concentrations of 0, 0.25%, 0.5% and 1.0% for 117–121 weeks, giving an average dose of 105–550.0 mg/kg bw per day. No abnormalities related to treatment were observed, with the exception of a very low incidence of hepatocarcinomas in female animals treated with the 1.0% dose (*37*).

The acute oral LD_{50} for anethole in rats was 2.09 g/kg bw; repeated oral doses of 695.0 mg/kg bw caused mild liver lesions consisting of slight discoloration, mottling, and blunting of the lobe edges (*38*).

Clinical pharmacology

No information available.

Adverse reactions

Occasional allergic reactions to Fructus Anisi affecting the skin, respiratory tract and gastrointestinal tract have been reported (*14*). Inhalation of powdered fruits induced an allergic effect in one subject with asthma. Skin-prick tests showed a positive reaction and the patient had a high level of specific anti-aniseed immunoglobulin E antibodies in his blood (*39*). Anethole toxicity in infants has been reported, and presents clinically with symptoms of hypertonia, continued crying, atypical ocular movements, twitching, cyanosis, vomiting and lack of appetite (*4, 40*).

Contraindications

Fructus Anisi is contraindicated in cases of known allergy to aniseed and anethole (*14, 39*). Owing to the traditional use of the oil as an emmenagogue and to induce labour, its experimental estrogenic and potential mutagenic effects, and reports of anethole toxicity in infants (*4, 40*), use of the dried fruits in pregnancy and nursing, and in children under the age of 12 years is contraindicated.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A 95% ethanol extract of Fructus Anisi, 10.0 mg/plate, was inactive in the *Salmonella*/microsome assay in *S. typhimurium* TA102 (*41*). Inconsistent

results have been reported concerning the mutagenicity of anethole in this assay. One group showed that it was mutagenic (*42*), another that it was not mutagenic in *S. typhimurium* strains TA1535, TA100 and TA98 (*43*). In a further study, *trans*-anethole (concentration not specified) did not increase the mutant frequency in the *Salmonella*/microsome assay, but did increase mutant frequency in the L5178Y mouse-lymphoma TK+/- assay in a dose-dependent manner, with metabolic activation (*40*). *Trans*-anethole did not induce chromosome aberrations in vitro in the Chinese hamster ovary cell assay (*40*). *Trans*-anethole was weakly hepatocarcinogenic in female rats when administered at a dose of 1% in the diet for 121 weeks; however, this effect is not mediated by a genotoxic event (*44*). *Trans*-anethole was investigated for its antifertility activity in rats, after intragastric administration of doses of 50.0 mg/kg bw, 70.0 mg/kg bw and 80.0 mg/kg bw (*45*). Anti-implantation activity of 100% was observed in animals treated with the highest dose. The compound has been reported to show estrogenic, antiprogestational, androgenic and antiandrogenic activities (*45*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms
Powdered dried fruits for oral infusions and other galenical preparations for internal use or inhalation (*14*). Store in a well-closed container, protected from heat and light.

Posology
(Unless otherwise indicated)
Average oral daily dose for internal use: Fructus Anisi 3.0 g; equivalent for other preparations (*14*).

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Semen Armeniacae

Definition

Semen Armeniacae consists of the dried ripe seeds of *Prunus armeniaca* L., *Prunus armeniaca* L. var. *ansu* Maxim. or allied species (Rosaceae) (*1–4*).

Synonyms

Armeniaca vulgaris Lam. (*5*).

Selected vernacular names

Abricotier, anzu, apricot, Aprikose, Aprikosenbaum, barqouq, bitter apricot, chuli, cuari, culu, elk mesmas, haeng-in, Himalayan wild apricot, hsing, ku-xinggren, kurbani, maó, michmich, mouchmouch, ó mai, sal-goo, touffah armani, wild apricot, xing ren, zardalou, zardalu (*3, 5–8*).

Geographical distribution

Indigenous to the Korean peninsula and to China, India and Japan (*9, 10*). Cultivated in Asia, North Africa and United States of America (*11*).

Description

A medium-sized, deciduous tree, with reddish bark and glabrous twigs. Leaves convoluted in bud, blade broadly ovate, 5–7 cm long, 4–5 cm wide, acuminate, crenate-glandular, hairy on the veins of the underside when young, glabrous when mature, except for the axils of the underside veins. Petiole approximately 2.5 cm long, glandular; stipules, lanceolate, glandular on the margins. Flowers appearing before the leaves, bisexual, pinkish to white, solitary or fascicled, pedicels very short; calyx-tube campanulate, puberulent, 5 mm long; surrounding lobes, pubescent, half the length of the tube; petals suborbicular, 7–13 mm long; stamens inserted with the petals at the mouth of the calyx-tube; ovary and base of the style hairy. Fruit a downy or glabrous, yellow-tinged, red drupe with a fleshy outer layer surrounding a hard stone containing the seed (*9, 10*).

Plant material of interest: dried ripe seeds

General appearance

Flattened, cordate, 1.1–1.9 cm long, 0.8–1.5 cm wide, 0.4–0.8 cm thick, acute at one end, plump, unsymmetrical, rounded at the other. Seed coat yellowish-brown to deep brown; short linear hilum situated at the acute end; chalaza at the rounded end, with numerous, deep-brown veins radiating upwards. Testa, thin; two cotyledons (*1, 3, 4*).

Organoleptic properties

Odourless; taste: bitter (*1, 3, 4*).

Microscopic characteristics

Epidermal surface has stone cells, 60–90 µm in diameter, on veins protruded by vascular bundles, which appear as angular circles–ellipses, approximately uniform in shape, with uniformly thickened walls. In lateral view, stone cells appear obtusely triangular, walls extremely thickened at the apex (*1, 2*).

Powdered plant material

See characteristic features under Microscopic characteristics (*1, 2*).

General identity tests

Macroscopic and microscopic examinations, and microchemical tests (*1, 2, 4*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

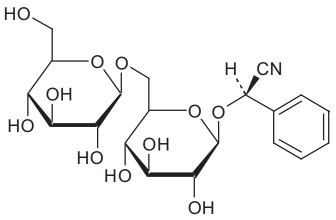
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, alcohol-soluble extractive, water-soluble extractive and loss on drying tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 3.0% amygdalin determined by titrimetric assay with silver nitrate (*4*). A high-performance liquid chromatography method is also available (*15*).

Major chemical constituents
The major constituent is amygdalin (up to 4.9%), a cyanogenic glycoside (a plant compound that contains sugar and produces cyanide). Other cyanogenic compounds present are prunasin and mandelonitrile. Also present are the amygdalin-hydrolysing enzyme, emulsin, and fatty acids and sitosterols (*8, 16*). The structure of amygdalin is presented below.

amygdalin



Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Internally as a decoction, after processing by dipping in boiling water and stir-frying until yellow (*4*), for symptomatic treatment of asthma, cough with profuse expectoration and fever. The seed oil is used for treatment of constipation (*3, 4*).

Uses described in traditional medicine
Treatment of gynaecological disorders, skin hyperpigmentation, headache and rheumatic pain (*8*). The seed oil is used in the form of eardrops for inflammation and tinnitus, and for treatment of skin diseases (*17*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activity

Intragastric administration of 46.32 mg/kg body weight (bw) of amygdalin to rats induced a small increase in body temperature, and prevented ephedrine-induced hyperthermia (*18*). In the hot plate and acetic acid-induced writhing tests in mice, the analgesic median effective doses (ED_{50}) were 457.0 mg/kg and 288.0 mg/kg bw, respectively. However, at these doses, amygdalin could not substitute for morphine in morphine-addicted rats in relieving withdrawal syndrome. No anti-inflammatory effects were observed in the animals treated with amygdalin (*19*).

Antitumour activity

Intragastric administration of 200.0 mg/kg–2.0 g/kg bw of amygdalin to mice with P388 lymphocytic leukaemia or P815 mast-cell leukaemia on days 1 and 5, or days 1, 5 and 9. Despite treatment with high doses of amygdalin there was no prolongation in the lifespan of mice in either group (*20*).

Antitussive activity

Amygdalin, 30.0 mg, had antitussive effects in the sulfur dioxide gas-induced cough model in mice (*21, 22*). The enzymes amygdalase and prunase, along with gastric juice, hydrolyse amygdalin to form small amounts of hydrocyanic acid, thereby stimulating the respiratory reflex and producing antitussive and antiasthmatic effects (*19*).

Metabolism and pharmacokinetics

After intragastric administration of 30.0 mg of amygdalin or prunasin to rats, capacity for hydrolysing these compounds was greatest in the organs of 15-day-old animals, most of the activity being concentrated in the tissues of the small and large intestines. The activity decreased with age. In adult rats, hydrolysis of prunasin was greater than that of amygdalin and was concentrated in the spleen, large intestine and kidney (35.0 µg, 15.0 µg and 8.9 µg of prunasin hydrolysed per hour per gram of tissue, respectively). Minced liver, spleen, kidney and stomach tissue had a greater hydrolytic capability than the homogenate of these organs, while the reverse was the case with the small and large intestines. Following oral administration of 30.0 mg of amygdalin to adult rats, distribution after the first hour was as follows: stomach 0.89 mg, small intestine 0.78 mg, spleen 0.36 mg, large intestine 0.30 mg, kidney 0.19 mg, liver 0.10 mg and serum 5.6 µg/ml. At the end of the second hour, the highest amygdalin content, 0.79 mg, was found in the large intestine (*23, 24*).

Toxicology

Intragastric administration of 125.0 mg/kg bw of powdered defatted Semen Armeniacae per day for 7 days to mice or rabbits produced no behavioural, histological or microscopic toxic effects (*25*). Intragastric administration of 250.0 mg/kg bw of an aqueous suspension of the powdered defatted seeds to mice had no toxic effects within a 24-hour period (*25*). The median lethal dose (LD_{50}) of amygdalin in rats was 880.0 mg/kg bw after intragastric administration. However, when a dose of 600.0 mg/kg bw was administered by the same route, together with β-glucosidase, all animals died. Total and magnesium adenosine triphosphatase activities in the heart decreased with increasing levels of administered amygdalin (*23, 24*).

Diets containing 10% ground seeds were fed to young and breeding male and female rats. The seeds were obtained from 35 specific apricot cultivars and divided into groups containing low amygdalin (cyanide < 50.0 mg/100 g), moderate amygdalin (cyanide 100–200.0 mg/100 g), or high amygdalin (cyanide > 200.0 mg/100 g). Growth of young male rats was greatest in the low and moderate amygdalin groups, indicating that the animals were more sensitive to the bitter taste of the kernels with high amygdalin content. In female rats, but not males, liver rhodanase activity and blood thiocyanate levels were increased with the high-amygdalin diet, but both males and females efficiently excreted thiocyanate, indicating efficient detoxification and clearance of cyanide hydrolysed from the dietary amygdalin. No other changes in blood chemistry were observed (*26*).

Toxic amounts of cyanide were released into the blood of rats following intragastric administration of amygdalin (proprietary laetrile) (dose not specified); cyanide blood concentrations and toxicity were lower when amygdalin was given intravenously (dose not specified). Analysis of the time course of cyanogenesis suggests that cyanide could accumulate in blood after repeated oral doses of amygdalin (*27*). Following intraperitoneal administration of 250.0 mg/kg bw, 500.0 mg/kg bw or 750.0 mg/kg bw of amygdalin per day to rats for 5 days, mortalities were 30.8%, 44.1% and 56.8%, respectively. The mode of death and the elevated serum cyanide levels in the dying animals strongly suggested cyanide poisoning as the cause of death (*28*).

The systemic effects of an oil prepared from the seeds containing 94% unsaturated fatty acids, and oleic and linoleic acids were assessed in a 13-week feeding study in rats. The animals were fed a diet containing 10% oil. No toxic effects were observed and no macroscopic or microscopic lesions in any of the organs were found (*29*). External applications of 0.5 ml of the seed oil to rabbits did not produce any observable toxic effects (*25*).

Clinical pharmacology

Antitumour activity

The term "laetrile" is an acronym used to describe a purified form of amygdalin, a cyanogenic glucoside found in the pits of many fruits and raw nuts and in other plants, such as lima beans, clover and sorghum (*30*). However, the chemical composition of a proprietary laetrile preparation patented in the United States of America (Laetrile®), which comprises mandelonitrile-β-glucuronide, a semisynthetic derivative of amygdalin, is different from that of natural laetrile/amygdalin, which consists of mandelonitrile β-D-gentiobioside and is made from crushed apricot pits. Mandelonitrile, which contains cyanide, is a structural component of both products. It has been proposed that the cyanide is an active anticancer ingredient in laetrile, but two other breakdown products of amygdalin, prunasin (which is similar in structure to the proprietary product) and benzaldehyde, have also been suggested. The studies discussed in this summary used either Mexican laetrile/amygdalin or the proprietary formulation. Laetrile can be administered orally as a pill, or it can be given by injection (intravenous or intramuscular). It is commonly given intravenously over a period of time followed by oral maintenance therapy. The incidence of cyanide poisoning is much higher when laetrile is taken orally because intestinal bacteria and some commonly eaten plants contain enzymes (β-glucosidases) that activate the release of cyanide following laetrile ingestion (*31*). Relatively little breakdown to yield cyanide occurs when laetrile is injected (*32*).

Laetrile has been used as an anticancer treatment in humans worldwide. While many anecdotal reports and case reports are available, results from only two clinical trials have been published (*33, 34*). No controlled clinical trial (a trial including a comparison group that receives no additional treatment, a placebo, or another treatment) of laetrile has ever been conducted. Case reports and reports of case series have provided little evidence to support laetrile as an anticancer treatment (*35*). The absence of a uniform documentation of cancer diagnosis, the use of conventional therapies in combination with laetrile, and variations in the dose and duration of laetrile therapy complicate evaluation of the data. In a published case series, findings from ten patients with various types of metastatic cancer were reported (*36*). These patients had been treated with a wide range of doses of intravenous proprietary laetrile (total dose range 9–133 g). Pain relief (reduction or elimination) was the primary benefit reported. Some responses, such as decreased adenopathy (swollen lymph nodes) and decreased tumour size, were noted. Information on prior or concurrent therapy was provided; however, patients were not followed

long-term to determine whether the benefits continued after treatment ceased. Another case series, published in 1953, included 44 cancer patients and found no evidence of objective response that could be attributed to laetrile (*37*). Most patients with reported cancer regression in this series had recently received or were receiving concurrent radiation therapy or chemotherapy. Thus, it is impossible to determine which treatment produced the positive results.

In 1978, the United States National Cancer Institute (NCI), at the National Institutes of Health, requested case reports from practitioners who believed their patients had benefited from laetrile treatment (*38*). Of the 93 cases submitted, 67 were considered suitable for evaluation. An expert panel concluded that only two of the 67 patients had complete responses, and that four others had partial responses while using laetrile. On the basis of these six responses, NCI agreed to sponsor phase I and phase II clinical trials. The phase I study was designed to test the doses, routes of administration and schedule of administration. Six patients with advanced cancer were treated with amygdalin given intravenously at 4.5 g/m^2 per day. The drug was largely excreted unchanged in the urine and produced no clinical or laboratory evidence of a toxic reaction. Amygdalin given orally, 0.5 g three times daily, produced blood cyanide levels of up to 2.1 µg/ml. No clinical or laboratory evidence of toxic reaction was seen in the six patients taking the drug at this dosage. However, two patients who ate raw almonds while undergoing oral treatment developed symptoms of cyanide poisoning (*33*).

In the phase II clinical trial, 175 patients with various types of cancer (breast, colon, lung) were treated with amygdalin plus a "metabolic therapy" programme consisting of a special diet, with enzymes and vitamins. The great majority of these patients were in good general condition before treatment. None was totally disabled or in a preterminal condition. One-third had not received any previous chemotherapy. The amygdalin preparations were administered by intravenous injection for 21 days, followed by oral maintenance therapy, dosages and schedules being similar to those evaluated in the phase I study. Vitamins and pancreatic enzymes were also administered as part of a metabolic therapy programme that included dietary changes to restrict the use of caffeine, sugar, meats, dairy products, eggs and alcohol. A small subset of patients received higher-dose amygdalin therapy and higher doses of some vitamins as part of the trial. Patients were followed until there was definite evidence of cancer progression, elevated blood cyanide levels or severe clinical deterioration. Among 175 patients suitable for assessment, only one met the criteria for response. This patient, who had gastric carcinoma with cervical lymph

node metastasis, experienced a partial response that was maintained for 10 weeks while on amygdalin therapy. In 54% of patients there was measurable disease progression at the end of the intravenous course of treatment, and all patients had progression 7 months after completing intravenous therapy; 7% reported an improvement in performance status (ability to work or to perform routine daily activities) at some time during therapy, and 20% claimed symptomatic relief. In most patients, these benefits did not persist. Blood cyanide levels were not elevated after intravenous amygdalin treatment; however, they were elevated after oral therapy (*34*). On the basis of this phase II study, NCI concluded that no further investigation of laetrile was warranted.

Adverse reactions

The side-effects associated with amygdalin treatment are the same as the symptoms of cyanide poisoning. Cyanide is a neurotoxin that initially causes nausea and vomiting, headache and dizziness, rapidly progressing to cyanosis (bluish discoloration of the skin due to oxygen-deprived haemoglobin in the blood), liver damage, marked hypotension, ptosis (droopy upper eyelid), ataxic neuropathies (difficulty in walking due to damaged nerves), fever, mental confusion, convulsions, coma and death. These side-effects can be potentiated by the concurrent administration of raw almonds or crushed fruit pits, eating fruits and vegetables that contain β-glucosidase, such as celery, peaches, bean sprouts and carrots, or high doses of vitamin C (*35*).

Numerous cases of cyanide poisoning from amygdalin have been reported (*39–42*). After ingestion, amygdalin is metabolized in the gastrointestinal tract to produce prunasin and mandelonitrile, which are further broken down to benzaldehyde and hydrocyanic acid, the latter of which is highly toxic. Overdose causes dizziness, nausea, vomiting and headache, which may progress to dyspnoea, spasms, dilated pupils, arrhythmias and coma. A 65-year-old woman with cirrhosis and hepatoma lapsed into deep coma, and developed hypotension and acidosis after ingestion of 3 g of amygdalin. After initial treatment, the patient regained consciousness, but massive hepatic damage led to her death (*42*). A 67-year-old woman with lymphoma suffered severe neuromyopathy following amygdalin treatment, with elevated blood and urinary thiocyanate and cyanide levels. Sural nerve biopsy revealed a mixed pattern of demyelination and axonal degeneration, the latter being prominent. Gastrocnemius muscle biopsy showed a mixed pattern of denervation and myopathy with type II atrophy (*41*).

Contraindications

Semen Armeniacae should not be administered during pregnancy or nursing, or to children (*43, 44*).

Warnings

Overdose may cause fatal intoxication (*4, 43, 44*). The lethal dose is reported to be 7–10 kernels in children and 50–60 kernels (approximately 30 g) in adults (*45*).

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

No effects on fertility were observed in rats fed a diet containing 10% Semen Armeniacae for 5 weeks (*26*). An aqueous extract of the seeds was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, or in the *Bacillus subtilis* H-17 recombinant assay at concentrations of up to 100.0 mg/ml (*46*). However, a hot aqueous extract of the seeds was mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 at a concentration of 12.5 mg/plate (*47*).

Pregnancy: teratogenic effects

Intragastric administration of amygdalin (dose not specified) to pregnant hamsters induced skeletal malformations in the offspring, and intravenous administration resulted in embryopathic effects. Oral laetrile increased in situ cyanide concentrations, while intravenous laetrile did not. Thiosulfate administration protected embryos from the teratogenic effects of oral laetrile. The embryopathic effects of oral laetrile appear to be due to cyanide released by bacterial β-glucosidase activity (*48*). A pregnant woman who took laetrile as daily intramuscular injections (dose not specified) during the last trimester gave birth to a live infant at term. There was no laboratory or clinical evidence of elevated cyanide or thiocyanate levels (*49*).

Pregnancy: non-teratogenic effects

Offspring of breeding rats fed a high-amygdalin diet (cyanide > 200.0 mg/100 g) for 18 weeks had lower 3-day survival indices, lactation indices and weaning weights than those in a low-amygdalin group (cyanide < 50.0 mg/100 g). This may indicate that the cyanide present in the milk may not be efficiently detoxified to thiocyanate and excreted by neonates (*26*).

Nursing mothers

See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms
Processed (see Posology) dried ripe seeds (*4*); seed oil. Store in a cool, dry place, protected from moths (*4*).

Posology
(Unless otherwise indicated)
Average daily dose: 3.0–9.0 g of dried ripe seeds processed by breaking into pieces, rinsing in boiling water and stir-frying until yellow, then adding to a decoction when nearly finished (*4*).

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Flos Arnicae

Definition

Flos Arnicae consists of the dried flower heads (capitula) of *Arnica montana* L. (Asteraceae) (*1–3*).

Synonyms

Doronicum arnica Desf., *D. montanum* Lam. (*4*). Asteraceae are also known as Compositae.

Selected vernacular names

Arnica, arnika, arnique, bétoine des montagnes, betouana, Bergwohlverleih, celtic bane, dokhanolfouh, Echtes Wolferlei, estourniga, estrunica, Fallkraut, Kraftwurz, leopard's bane, mountain arnica, mountain tobacco, St Luzianskraut, Stichwurzel, strunica, Verfangkraut, Wohlverleih, wolf's bane, Wundkraut (*4–9*).

Geographical distribution

Indigenous to central Europe. Widely cultivated around the world (*1, 4, 7*).

Description

A perennial herb, 20–50 cm high. Aerial portion consists of a basal rosette of entire oblanceolate leaves up to 17 cm long, five to seven veins, from the centre of which projects an erect, simple, glandular hairy stem up to 0.6 m high. Stem bears two to four pairs of cauline leaves, ovate, elliptic-oblong, lanceolate or oblanceolate, with rounded or rounded-toothed apex and clothed with numerous nonglandular and glandular hairs, up to 16 cm long and 5 cm wide. Peduncles, one to three, bearing alternate bracteoles, extending from the uppermost pair of cauline leaves; glandular–puberulent, each terminating in a hemispherical or turbinate capitulum bearing orange-yellow flowers, which are tubular. Fruits, black to brown, five-ribbed, with a bristle tuft of hairs (*5, 8*).

Plant material of interest: dried flower heads

General appearance

Capitulum about 20 mm in diameter and 15 mm deep, with a peduncle 2–3 cm long. Involucre with 18–24 elongated lanceolate bracts, 8–10 mm long with acute apices, arranged in one or two rows, green with yellowish-green external hairs visible under a lens. Receptacle, about 6 mm in diameter, convex, alveolate and covered with hairs; periphery bears about 20 ligulate florets 20–30 mm long; disc bears a greater number of tubular florets about 15 mm long. Ovary, 4–8 mm long, crowned by a pappus of whitish bristles 4–8 mm long. Some brown achenes, crowned or not by a pappus, may be present (*3*).

Organoleptic properties

Odour: characteristic aromatic (*1, 3, 5*); taste: bitter and acrid (*1, 5*).

Microscopic characteristics

Epidermis of corolla papillose, containing yellow-orange globular masses, some cells also containing dark brown–black patches of phytomelan; base of corolla tube of ligulate florets with uniseriate covering trichomes of four to six cells, up to 1 mm in length; bristles of pappus four to six cells in diameter and barbed by exertion of the pointed cell apices. Cells of ovary or fruit walls contain abundant black patches of phytomelan. Corolla and ovary wall with numerous composite glandular trichomes; ovary wall with numerous appressed twin hairs each composed of two narrow parallel cells diverging at the tips. Pollen grains spiky, spherical 35–52 µm in diameter, with finely granular exine, spines up to 8 µm long, three pores and furrows (*1*).

Powdered plant material

Light yellowish-brown to light olive-brown. Epidermis of the involucre bracts with stomata and trichomes, which are more abundant on the outer surface. Trichomes include: uniseriate multicellular covering trichomes, 50–500 µm long, particularly abundant on the margins; secretory trichomes about 300.0 µm long with uni- or biseriate multicellular stalks and with multicellullar, globular heads, abundant on the outer surface; similar trichomes, 80.0 µm long, abundant on the inner surface of the bract. Epidermis of the ligulate corolla consists of lobed or elongated cells, a few stomata and trichomes of different types: covering trichomes, with very sharp ends, whose length may exceed 500 µm; secondary trichomes with multicellular stalks and multicellular globular heads. Ligule ends in rounded papillose cells. Epidermis of the ovary covered with trichomes: secondary trichomes with short stalks and multicellular globular

heads; twinned covering trichomes usually consisting of two longitudinally united cells, with common punctuated walls, their ends sharp and sometimes bifid. Epidermis of the calyx consists of elongated cells bearing short, unicellular, covering trichomes pointing towards the upper end of the bristle. Pollen grains, about 30 µm in diameter, rounded, with spiny exine, and three germinal pores (*3*).

General identity tests

Macroscopic and microscopic examinations (*1, 3–5*), and thin-layer chromatography for phenolic compounds (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 5.0% (*3*).

Total ash

Not more than 10% (*3*).

Acid-insoluble ash

Not more than 1.2% (*11*).

Sulfated ash

Not more than 13% (*2*).

Water-soluble extractive

Not less than 17% (*2*).

Alcohol-soluble extractive

Not less than 15% using 45% ethanol (*1*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European Pharmacopoeia*

(*12*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Chemical tests to be established in accordance with national requirements.

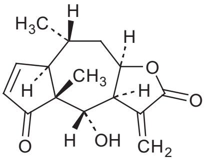
Chemical assays

Contains not less than 0.40% of total sesquiterpene lactones calculated as helenalin tiglate, determined by high-performance liquid chromatography (*3*).

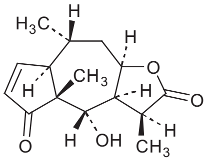
Major chemical constituents

The major constituents include the essential oil (0.5%), fatty acids (content not specified), thymol (content not specified), pseudoguaianolide sesquiterpene lactones (0.2–0.8%) and flavonoid glycosides (0.2–0.6%) (*4, 9, 14*). The primary sesquiterpene lactones are helenalin, 11α,13-dihydrohelenalin and their fatty acid esters. Flavonoids include glycosides and/or glucuronides of spinacetin, hispidulin, patuletin and isorhamnetin, among others (*4, 7, 9, 14–16*). The structures of helenalin and 11α,13-dihydrohelenalin are presented below.

helenalin



11α,13-dihydrohelenalin



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

As a topical counterirritant for treatment of pain and inflammation resulting from minor injuries and accidents, including bruises, ecchymoses,

haematomas and petechiae (*1, 17*). Treatment of inflammation of the oral mucous membranes, insect bites and superficial phlebitis (*17*).

Uses described in traditional medicine

Treatment of indigestion, cardiovascular disease, and rheumatism. As an emmenagogue (*9*).

Pharmacology

Experimental pharmacology

Analgesic and anti-inflammatory activity

In vitro, helenalin, 5.0 µmol/l, significantly ($P < 0.01$) suppressed the activity of prostaglandin synthetase in mouse and rat homogenates, and human polymorphonuclear neutrophils, indicating an anti-inflammatory effect (*18*). Human polymorphonuclear neutrophil chemotaxis was inhibited by helenalin, 5.0 µmol/l, in vitro. It was concluded that the α-methylene-γ-lactone moiety played a role in the anti-inflammatory activity of this compound (*18*). Helenalin, 4.0 µmol/l, selectively inhibited the transcription factor nuclear factor (NF)-κβ (*19*).

Intragastric administration of 100.0 mg/kg body weight (bw) of an 80% ethanol extract of Flos Arnicae reduced carrageenan-induced hind paw oedema by up to 29% in rats (*20*). Intraperitoneal administration of 2.5–5.0 mg/kg bw of helenalin significantly ($P < 0.001$) inhibited carrageenan-induced hind paw oedema in rats by 77% after 72 hours (*21*). Intraperitoneal administration of 20.0 mg/kg bw of helenalin strongly inhibited acetic acid-induced writhing by 93% in mice but did not have analgesic effects in mice in the hot-plate test. Intraperitoneal administration of 2.5 mg/kg bw of helenalin to rats inhibited arthritis induced by *Mycobacterium butyricum* by 87% (*21*).

Antioxidant activity

The effect of a tincture of Flos Arnicae on lipid peroxidation and glutathione metabolism in rat liver was assessed following induction of hepatitis by the administration of carbon tetrachloride. Intragastric administration of 0.2 ml/g bw of the tincture to rats decreased the rate of lipid oxidation and increased the activities of the enzymes involved in glutathione metabolism (*22*). Intragastric administration of 0.2 ml/g bw of the tincture per day for 14 days to rats with hepatitis induced by carbon tetrachloride led to a normalization of the hydrolytic enzymes (*23*).

Antitumour activity

Helenalin is cytotoxic to a wide variety of cancer cell lines in vitro, with a median effective dose (ED_{50}) range of 0.03–1.0 µg/ml (*24–27*). Intraperi-

toneal administration of 1.5–33.3 mg/kg bw of helenalin to mice and rats had antitumour activity against a variety of chemically induced tumours (*28–30*).

Cardiovascular effects

Flos Arnicae and extracts of the flower heads have cardiotonic and hypotensive effects in various animal models. Intravenous administration of a single dose of 1.0 ml of a tincture of the flower heads to rabbits had negative chronotropic effects and reduced blood pressure (*31*). Intravenous administration of 1.0 ml of an aqueous or 95% ethanol extract of the flower heads had cardiotonic effects in frogs, and a tincture demonstrated hypotensive activity in rabbits after intravenous administration of 1.0 ml (*32, 33*). A 30% ethanol extract of the flower heads, 0.1–0.3% in the bath medium, had positive inotropic effects in isolated guinea-pig hearts (*33*). Intravenous administration of 5.0 g/kg bw of a fluid extract or tincture of the flower heads increased the blood pressure of cats and guinea-pigs (*34*).

Helenalin, 50.0 µg/ml, decreased intracellular calcium levels in cultured fibroblasts, and potentiated the responses induced by vasopressin and bradykinin (*35*). Intravenous administration of helenalin had cardiotoxic effects in mice (25.0 mg/kg bw) and dogs (90.0 mg/kg bw) (*36*).

Choleretic activity

Intravenous administration of 1.0 ml of a 95% ethanol extract of the flower heads to dogs increased bile secretion by 25–120% (*37*). Intragastric administration of a hot aqueous extract of the flower heads had choleretic effects in rats (dose not specified) (*38*) and dogs (50.0 ml/animal) (*39*).

Toxicology

The oral median lethal dose (LD_{50}) of a 30% ethanol extract of the flower heads was 37.0 ml/kg in mice (*33*). The intragastric LD_{50} for helenalin has been established for numerous species: mice 150.0 mg/kg bw, rats 125.0 mg/kg bw, rabbits 90.0 mg/kg bw, hamsters 85.0 mg/kg bw and ewes 125.0 mg/kg bw (*40*).

Uterine stimulant effects

Intragastric administration of a tincture of the flower heads (dose not specified) had uterine stimulant effects in guinea-pigs (*41*). Intragastric administration of a hot aqueous extract of the flower heads (dose not specified) stimulated uterine contractions in rats (*38*).

Clinical pharmacology

No information available. Clinical trials of homeopathic preparations were not assessed.

Adverse reactions

Numerous cases of dermatitis of toxic or allergic origin have been reported (*42*), usually following prolonged, external application of a tincture of Flos Arnicae. The compounds responsible for the hypersensitivity reaction are the sesquiterpene lactones helenalin and helenalin acetate (*43*). Cross-reactivity to other Asteraceae flowers has been reported (*44–47*).

The flower heads are irritant to the mucous membranes and ingestion may result in gastroenteritis, muscle paralysis (voluntary and cardiac), an increase or decrease in pulse rate, heart palpitations, shortness of breath and death. A fatal case of poisoning following the ingestion of 70.0 g of a tincture of the flower heads has been reported (*48*).

A case of severe mucosal injuries following the misuse of an undiluted mouth rinse with a 70% alcohol content, which also contained oil of peppermint and Flos Arnicae, has been reported (*49*).

Contraindications

Flos Arnicae is used in traditional systems of medicine as an emmenagogue (*9*), and its safety during pregnancy and nursing has not been established. Therefore, in accordance with standard medical practice, the flower heads should not be administered to pregnant or nursing women. Flos Arnicae is also contraindicated in cases of known allergy to *Arnica* or other members of the Asteraceae (Compositae) (*37, 42, 50, 51*).

Warnings

A fatal case of poisoning following the ingestion of 70.0 g of a tincture of Flos Arnicae has been reported (*48*). Internal use of Flos Arnicae or extracts of the flower heads is not recommended. For external use only. Do not apply to open or broken skin. Keep out of the reach of children (*17*).

Precautions

General

Avoid excessive use. Chronic, frequent external applications may induce allergy-related skin rashes with itching, blister formation, ulcers and superficial necrosis. Prolonged treatment of damaged or injured skin or indolent leg ulcers may induce the formation of oedematous dermatitis with the formation of pustules (*17*).

Carcinogenesis, mutagenesis, impairment of fertility

Helenalin has cytotoxic effects in vitro (see Experimental pharmacology). However, in the *Salmonella*/microsome assay, helenalin was not muta-

genic in *S. typhimurium strains* TA102, TA98 or TA100 at concentrations of up to 30 µg/ml (*52, 53*).

Pregnancy: teratogenic effects
Intraperitoneal administration of 6.0–20.0 mg/kg bw of helenalin was not teratogenic in mice (*21*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Warnings. For external use only. Do not apply to abraded or broken skin.

Other precautions
No information available on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms
Dried flower heads and other galenical preparations. Store protected from light and moisture (*7*).

Posology
(Unless otherwise indicated)
For external applications only, apply undiluted externally on the affected area two or three times daily: infusion for compresses, 2 g of Flos Arnicae per 100 ml water; tincture for compresses, one part Flos Arnicae to 10 parts 70% ethanol; mouth rinse, 10-fold dilution of tincture, do not swallow; ointment, 20–25% tincture of Flos Arnicae or not more than 15% essential oil (vehicle not specified) (*17*).

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Folium Azadirachti

Definition

Folium Azadirachti consists of the dried leaves of *Azadirachta indica* A. Juss. (Meliaceae) (*1–4*).

Synonyms

Melia azadirachta L., *M. indica* (A. Juss.) Brand., *M. indica* Brand. (*1–3*).

Selected vernacular names

Abodua, aforo-oyinbo, anwe egyane, arista, azad dirakht, azadarakht, azedarach, bead tree, bevinama, bevu, bewina mara, bodetso, bo-nim, cape lilac, chajara hourra, chichaâne arbi, China berry, China tree, cót anh, darbejiya, dogo yaro, dogo'n yaro, dogonyaro, dogoyaro, dongo yaro, dua gyane, gori, gringging, holy tree, igi-oba, imba, Indian lilac, Indian lilac tree, Indian neem tree, Indian sadao, Intaran, isa-bevu, jaroud, kahibevu, kingtsho, kiswahhili, kohhomba, kohumba, koummar, kuman masar, kuman nasara, kwinin, labkh, lilac de perse, lilas des indes, liliti, limb, limba, limbado, limado, linigbe, mahanim, mahanimba, mahnimu, mak tong, margosa, margosa tree, margose, marrar, mimba, mindi, miro tahiti, mwarobaini, neeb, neem, neem sikha, nim, nim tree, nimba, nimba-tikta, nimgach, nivaquine, ogwu akom, oilevevu, ouchi, Persian lilac, phãk kã dão, picumarda, sa-dao, sa-dao baan, sadao India, sdau, salien, sandan, sandannoki, sãu dâu, senjed talhk, shajarat el horrah, shereesh, tâak, tâakhak, touchenboku, vembu, vemmu, vepa, veppam, veppu, white cedar, xoan dào, zanzalakht, zaytoon (*1–9*).

Geographical distribution

Indigenous to India, and widely distributed in South and South-East Asia. Cultivated in Africa, the South Pacific Islands, South and Central America and Australia, and in southern Florida and California, United States of America (*1–3, 8–11*).

Description

A straight-boled deciduous tree 6–25 m high. Bark dark-brown, externally fissured, with a buff inner surface, fibrous fracture. Leaves alternately arranged, pinnately compound, up to 40 cm long, composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Inflorescences axillary panicles; flowers numerous, white, pedicillate, about 1.0 cm wide. Fruits yellowish drupes, oblong, about 1.5 cm long, containing thin pulp surrounding a single seed. When bruised, leaves and twigs emit an onion-like odour (*1–3, 8, 11*).

Plant material of interest: dried leaves

Other plant parts used, but not included in this monograph: flowers, seeds, stem bark, oil (*1–3, 8, 10, 12*).

General appearance

Compound leaves up to 40 cm long composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Glabrous dark green upper surface, paler underside (*1–3*).

Organoleptic properties

Odour: characteristic, alliaceous; taste: bitter (*1–3*).

Microscopic characteristics

Lower epidermis with anomocytic stomata and occasional unicellular trichomes. Two layers of palisade cells are found below the upper epidermis. Spongy parenchyma exhibits intercellular spaces and secretory cells, which are abundant on the borderline with the palisade cells. Anticlinal cell walls are almost straight. Mesophyll contains rosette crystals. Collenchyma interrupts mesophyll on both upper and lower surfaces in the midrib region. Vascular bundles strongly curved, lignified, collateral (*1–3*).

Powdered plant material

Green and characterized by the presence of cortical cells of the rachis, fragments of palisade cells, hairs, fibres, wood fibres, spiral lignified vascular elements, epidermal tissues of the leaf with characteristic anomocytic stomata and large pit cells with intercellular spaces. Epidermal cell walls straight (*2, 3*).

General identity tests
Macroscopic and microscopic examinations (*1–3*), microchemical tests (*2*) and thin-layer chromatography (*2*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter
Not more than 2% (*4*).

Total ash
Not more than 10% (*4*).

Acid-insoluble ash
Not more than 1% (*4*).

Water-soluble extractive
Not less than 19% (*4*).

Alcohol-soluble extractive
Not less than 13% (*4*).

Loss on drying
Not more than 3% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

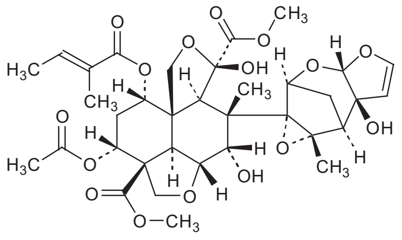
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

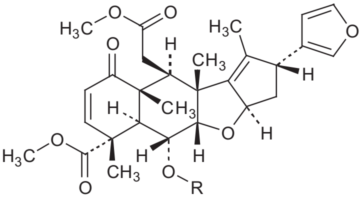
Other purity tests
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
High-performance liquid chromatography methods are available for the quantitative determination of oxidized tetranortriterpenes (*16, 17*).

Major chemical constituents
The major characteristic constituents are oxidized tetranortriterpenes including azadirachtin (azadirachtin A), 3-tigloylazadirachtol (azadirachtin B), 1-tigloyl-3-acetyl-11-hydroxy-meliacarpin (azadirachtin D), 11-demethoxycarbonyl azadirachtin (azadirachtin H), 1-tigloyl-3-acetyl-11-hydroxy-11-demethoxycarbonyl meliacarpin (azadirachtin I), azadiriadione, azadirachtanin, epoxyazadiradione, nimbin, deacetylnimbin, salannin, azadirachtolide, isoazadirolide, margosinolide, nimbandiol, nimbinene, nimbolin A, nimbocinone, nimbocinolide, nimbolide, nimocin, nimocinol and related derivatives (*9, 11, 18–20*). The structures of azadirachtin, nimbin and deacetylnimbin are presented below.



azadirachtin



nimbin R = CO-CH_3

deacetylnimbin R = H

Medicinal uses
Uses supported by clinical data
External applications for treatment of ringworm (*21*). However, data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents
Treatment of worm and lice infections, jaundice, external ulcers, cardiovascular disease, diabetes, gingivitis, malaria, rheumatism and skin disorders. External applications for treatment of septic wounds and boils (*6, 8*).

Uses described in traditional medicine

Treatment of allergic skin reactions, asthma, bruises, colic, conjunctivitis, dysentery, dysmenorrhoea, delirium in fever, gout, headache, itching due to varicella, jaundice, kidney stones, leprosy, leukorrhoea, psoriasis, scabies, smallpox, sprains and muscular pain, syphilis, yellow fever, warts and wounds (*10, 22*). Also used as an antivenin, contraceptive, emmenagogue, tonic, stomatic and vermicide (*9*).

Pharmacology

Experimental pharmacology

Anxiolytic and analgesic activities

Intragastric administration of 10.0–200.0 mg/kg body weight (bw) of an aqueous extract of Folium Azadirachti produced anxiolytic effects similar to those of 1.0 mg/kg bw of diazepam in rats in the elevated-plus-maze and open-field behaviour tests (*23*).

The analgesic effect of an extract of the leaves was assessed in mice using the acetic acid writhing test and the tail flick test. Intragastric administration of 10.0–100.0 mg/kg bw of the extract reduced the incidence of writhing and enhanced tail-withdrawal latencies (*24*).

Antiandrogenic activity

Intragastric administration of 20.0 mg, 40.0 mg or 60.0 mg of powdered leaves per day to rats for 24 days resulted in a decrease in the weight of the seminal vesicles and ventral prostate, and a reduction in epithelial height, nuclear diameter and secretory material in the lumen of these organs. Decreases in total protein and acid phosphatase activities were also observed. These regressive histological and biochemical changes suggest that the leaves have an antiandrogenic property (*25*). Histological and biochemical changes were also observed in the caput and cauda epididymis of rats treated orally with similar doses of the powdered leaves given daily for 24 days. The height of the epithelium and the diameter of the nucleus in both regions were reduced. Serum testosterone concentrations were also reduced in animals receiving the highest dose (*26*). Intragastric administration of an aqueous extract of the leaves (dose not specified) to male mice daily for 10 weeks resulted in a significant ($P < 0.01$) reduction in total serum testosterone and bilirubin (*27*).

Antihepatotoxic activity

The effect of an aqueous extract of the leaves was evaluated in paracetamol-induced hepatotoxicity in rats. Intragastric administration of 500.0 mg/kg bw of the extract significantly ($P < 0.01$) reduced elevated levels of serum

aspartate aminotransferase, alanine aminotransferase and γ-glutamyl transpeptidase (*28*).

Anti-inflammatory activity

Intragastric administration of 200.0 mg/kg bw of an aqueous extract of the leaves to rats decreased inflammation and swelling in the cotton pellet granuloma assay (*29*). Intraperitoneal injection of 200.0–400.0 mg/kg bw of an aqueous extract of the leaves to rats reduced carrageenan-induced footpad oedema (*30*).

Antihyperglycaemic activity

A hypoglycaemic effect was observed in normal and alloxan-induced diabetic rabbits after administration of 50.0 mg/kg bw of an ethanol extract of the leaves. The effect was more pronounced in diabetic animals, and reduced blood glucose levels. The hypoglycaemic effect was comparable to that of glibenclamide. Pretreatment with the extract 2 weeks prior to alloxan treatment partially prevented the rise in blood glucose levels as compared with control diabetic animals (*31*). Intragastric administration of 50.0–400.0 mg/kg bw of a 70% ethanol extract of the leaves significantly ($P < 0.001$) reduced elevated blood glucose levels in normal and streptozocin-induced diabetic rats (*32–34*). A 70% ethanol extract of the leaves significantly ($P < 0.05$) blocked the inhibitory effect of serotonin on insulin secretion mediated by glucose in isolated rat pancreas (*35*).

Antimalarial activity

An aqueous or ethanol extract of the leaves inhibited the growth of *Plasmodium falciparum* in vitro, with median inhibitory concentrations of 115.0 μg/ml and 5.0 μg/ml, respectively. Nimbolide, a constituent of the extract, inhibited the growth of *P. falciparum* in vitro with a median effective concentration of 2.0 μg/ml (*36*). However, intragastric administration of 746.0 mg/kg bw of the aqueous extract, 62.5 mg/kg bw of the ethanol extract or 12.5 mg/kg bw of nimbolide had no such effect in *Plasmodium*-infected mice (*36*). *P. berghei*-infected mice showed parasite suppression after intragastric administration of 125.0–500.0 mg/kg bw of a dried methanol extract of the leaves per day for 4 days, but all the animals died after 5 days (*37*). A 95% ethanol extract of the leaves at concentrations of up to 500.0 mg/ml did not inhibit the growth of *P. falciparum* in vitro (*38*).

Antimicrobial and antiviral activity

A methanol extract of the leaves, 1.0 mg/ml, inhibited plaque formation in six antigenic types of coxsackievirus B at 96 hours in vitro. The minimal inhibitory concentrations were not toxic to Vero African green mon-

key kidney cells. The subtoxic concentration was 8.0 mg/ml and the cytotoxic concentration was 10.0 mg/ml (*39*).

An aqueous extract of the leaves, at various concentrations depending on the organism, inhibited the growth of *Bacteroides gingivalis*, *B. intermedius, Streptococcus salivarius* and *S. viridans* in vitro (*40*). A petroleum ether extract of the leaves, at various concentrations depending on the organism, inhibited the growth of *Epidermophyton floccosum, Microsporum canis, M. gypseum, Trichophyton concentricum, T. violaceum* and *T. rubrum* (*41*).

Antioxidant activity

The effect of the leaves on hepatic lipid peroxidation and antioxidant status during gastric carcinogenesis induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine was assessed in rats. Intragastric administration of 100.0 mg/kg bw of an aqueous extract of the leaves decreased lipid peroxidation in the liver of tumour-bearing animals, which was accompanied by a decrease in the activities of glutathione peroxidase, glutathione-*S*-transferase and γ-glutamyl transpeptidase, and a reduction in glutathione level. Administration of 100.0 mg/kg bw of an extract of the leaves suppressed lipid peroxidation and increased hepatic levels of glutathione and glutathione-dependent enzymes (*42*). Intragastric administration of 100.0 mg/kg bw of an aqueous extract of the leaves three times per week to hamsters with buccal pouch carcinogenesis induced by 7,12-dimethylbenz[α]anthracene reduced lipid peroxidation and increased the glutathione concentration in the oral mucosa of tumour-bearing animals (*43*).

Antiulcer activity

The antiulcer effects of an aqueous extract of the leaves were investigated in rats exposed to 2-hour cold-restraint stress or given ethanol for 1 hour. The extract, administered orally in doses of 10.0 mg/kg bw, 40.0 mg/kg bw or 160.0 mg/kg bw as single- or five-dose pretreatments produced a dose-dependent reduction in the severity of gastric ulcers induced by stress and a decrease in gastric mucosal damage provoked by ethanol. The extract prevented mast cell degranulation and increased the amount of adherent gastric mucus in stressed animals (*44*). Intragastric administration of 40.0 mg/kg bw of an aqueous extract of the leaves per day for 5 days to rats inhibited stress-induced depletion of gastric wall adherent cells and mucus production (*44*).

Cardiovascular effects

Intragastric administration of 200.0 mg/kg bw of an alcohol extract of the leaves to anaesthetized rabbits decreased the heart rate from 280 to

150 beats per minute, and had a weak antiarrhythmic effect against ouabain-induced dysrhythmia (*45*). Intravenous administration of 100.0 mg/kg bw, 300.0 mg/kg bw or 1000.0 mg/kg bw of an ethanol extract of the leaves to rats resulted in initial bradycardia followed by cardiac arrhythmias. The treatment produced a dose-related fall in blood pressure that was immediate, sharp and persistent. Pretreatment with atropine or mepyramine failed to prevent the hypotensive effect of the extract (*46*).

Immune effects

The effect of an aqueous extract of the leaves on humoral and cell-mediated immune responses was assessed in mice treated with ovalbumin. At doses of 10.0 mg/kg bw, 30.0 mg/kg bw or 100.0 mg/kg bw, the extract produced no appreciable effects on organ/body weight indices for liver, spleen and thymus compared with controls. In tests for humoral immune responses, IgM and IgG levels, and antiovalbumin antibody titres were higher in mice receiving the highest dose of extract than in animals in the control group. In tests for cell-mediated immune responses, mice receiving the highest dose of extract showed enhancement of macrophage migration inhibition and footpad thickness (*47*). Intragastric administration of 100.0 mg/kg bw of an aqueous extract of the leaves to normal and stressed rats lowered blood glucose and triglyceride levels, attenuated stress-induced elevations of cholesterol and urea, and suppressed humoral responses (*48*).

The effect of powdered leaves on humoral and cell-mediated immune responses was assessed in chickens infected with infectious bursal disease. A dose of 2.0 g/kg bw per day given in the diet increased antibody titres against Newcastle disease virus antigen and enhanced inflammatory reactions to chloro-2,4-dinitrobenzene in the skin contact test (*49*).

Toxicology

Chickens fed diets containing the powdered leaves, 2% or 5%, from the 7th to the 35th day of age, and then a control diet for 2 weeks, showed a reduction in body weight gain and efficiency of feed use compared with controls. The main pathological changes observed included an increase in lactic dehydrogenase, glutamic-oxaloacetic transaminase and alkaline phosphatase activities, an increase in uric acid and bilirubin concentrations, and a decrease in total serum protein levels. There were marked reductions in the values of erythrocyte count, haemoglobin concentration, packed cell volume, mean corpuscular volume and mean corpuscular haemoglobin, which were associated with yellow discoloration on the legs and hepatonephropathy (*50*).

Intragastric administration of 50.0 mg/kg bw or 200.0 mg/kg bw of aqueous suspensions of the leaves per day to goats and guinea-pigs over a period of up to 8 weeks produced a progressive decrease in body weight, weakness, inappetence, loss of condition and decreases in the pulse and respiratory rates. In goats, the higher dose produced tremors and ataxia during the last few days of treatment. No statistically significant haematological changes were observed, although there was a tendency towards lowered erythrocyte counts, packed cell volume and haemoglobin levels. The treatment increased aspartate transferase and sorbitol dehydrogenase activities, and concentrations of cholesterol, urea, creatinine and potassium in the plasma. No significant changes in the plasma concentrations of sodium, chloride or bilirubin were detected. Autopsy of treated goats revealed areas of haemorrhagic erosion. The hearts appeared flappy and in some animals there was hydropericardium. Histopathologically, there was evidence of various degrees of haemorrhage, congestion, and degeneration in the liver, kidney, lung, duodenum, brain and seminiferous tubules (*51*).

The effect of intragastric administration of 40.0 mg/kg bw and 100.0 mg/kg bw of an aqueous extract of the leaves per day for 20 days on thyroid function was assessed in male mice. The higher dose decreased serum tri-iodothyronine and increased serum thyroxine concentrations. There was a concomitant increase in hepatic lipid peroxidation and a decrease in glucose-6-phosphatase activity. The lower dose produced no significant changes (*52*).

The median lethal dose of a 50% ethanol extract of the leaves in mice was 681.0 mg/kg bw when administered by intraperitoneal injection (*53*).

Clinical pharmacology

A 70% ethanol extract of the leaves was used for the treatment of ringworm in seven patients. External applications of a 40% solution of the extract twice per day to the affected areas for 5–10 days were reported to be effective (no further details available) (*21*).

Adverse reactions

A case of ventricular fibrillation and cardiac arrest due to neem leaf poisoning has been reported (*54–56*). Contact dermatitis has also been reported (*57*).

Contraindications

Owing to potential genotoxic effects (*58*), the leaves should not be administered during pregnancy or nursing, or to children under the age of 12 years.

Warnings
No information available.

Precautions
Drug interactions
Administration of Folium Azadirachti may reduce blood glucose levels and should therefore be used with caution in insulin-dependent diabetic patients or patients taking oral antihyperglycaemic drugs.

Carcinogenesis, mutagenesis, impairment of fertility
A petroleum ether extract of the leaves was not mutagenic in the *Salmonella*/microsome assay at concentrations of 0.1 ml/plate using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 (*59*).

Intragastric administration of 5.0 mg/10 g bw, 10.0 mg/10 g bw or 20.0 mg/10 g bw of an ethanol extract of the leaves per day for 7 days to mice significantly ($P < 0.05$) increased the incidence of structural and mitotic disruptive changes in metaphase chromosomes of bone marrow cells on days 8, 15 and 35 (*58*). Intragastric administration of 100.0 mg/kg bw of an ethanol extract of the leaves per day for 21 days had no effect on spermatogenesis in male rats, and no effect on implantation in female animals mated with treated males (*60*).

Pregnancy: teratogenic effects
Intragastric administration of 200.0 mg/kg bw of an acetone or 50% ethanol extract of the leaves to pregnant rats on days 1–7 of pregnancy did not produce any teratogenic or embryotoxic effects (*61*).

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test reactions; or non-teratogenic effects in pregnancy.

Dosage forms
Dried leaves for infusions and decoctions, and extracts and tinctures (*8*). Store leaves in a cool, dry place (*3*).

Posology

(Unless otherwise indicated)

Infusion (1:20): 15–30 ml. Tincture (1:5): 4–8 ml (*8*). External applications: 70% ethanol extract of the leaves diluted to 40%, apply twice daily (*21*).

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Oleum Azadirachti

Definition
Oleum Azadirachti consists of the fixed oil obtained from dried seeds of *Azadirachta indica* A. Juss. (Meliaceae).

Synonyms
Melia azadirachta L., *M. indica* (A. Juss.) Brand., *M. indica* Brand. (*1–3*).

Selected vernacular names
Abodua, aforo-oyinbo, anwe egyane, arista, azad dirakht, azadarakht, azedarach, bead tree, bevinama, bevu, bewina mara, bodetso, bo-nim, cape lilac, chajara hourra, chichaâne arbi, China berry, China tree, cót anh, darbejiya, dogo yaro, dogo'n yaro, dogonyaro, dogoyaro, dongo yaro, dua gyane, gori, gringging, holy tree, igi-oba, imba, Indian lilac, Indian lilac tree, Indian neem tree, Indian sadao, Intaran, isa-bevu, jaroud, kahibevu, kingtsho, kiswahhili, kohhomba, kohumba, koummar, kuman masar, kuman nasara, kwinin, labkh, lilac de perse, lilas des indes, liliti, limb, limba, limbado, limado, linigbe, mahanim, mahanimba, mahnimu, mak tong, margosa, margosa tree, margose, marrar, mimba, mindi, miro tahiti, mwarobaini, neeb, neem, neem sikha, nim, nim tree, nimba, nimbatikta, nimgach, nivaquine, ogwu akom, oilevevu, ouchi, Persian lilac, phãk kã dão, picumarda, sa-dao, sa-dao baan, sadao India, sdau, salien, sandan, sandannoki, sãu dâu, senjed talhk, shajarat el horrah, shereesh, tâak, tâakhak, touchenboku, vembu, vemmu, vepa, veppam, veppu, white cedar, xoan dào, zanzalakht, zaytoon (*1–9*).

Geographical distribution
Indigenous to India, and widely distributed in South and South-East Asia. Cultivated in Africa, the South Pacific Islands, South and Central America and Australia, and in southern Florida and California, United States of America (*1–3, 7, 10, 11*).

Description
A straight-boled deciduous tree 6–25 m high. Bark dark-brown, externally fissured, with a buff inner surface, fibrous fracture. Leaves alter-

nately arranged, pinnately compound, up to 40 cm long, composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Inflorescences axillary panicles; flowers numerous, white, pedicillate, about 1.0 cm wide. Fruits yellowish drupes, oblong, about 1.5 cm long, containing thin pulp surrounding a single seed. When bruised, leaves and twigs emit an onion-like odour (*1–3, 7, 11*).

Plant material of interest: fixed oil

General appearance
No information available.

Organoleptic properties
Odour: characteristic alliaceous (*10*); taste: no information available.

General identity tests
Macroscopic examination and thin-layer chromatography (*2*).

Purity tests

Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Chemical
Relative density 0.913–0.919 (*13*); refractive index 1.462–1.466 (*13*); saponification value 196.0 (*13*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*15*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

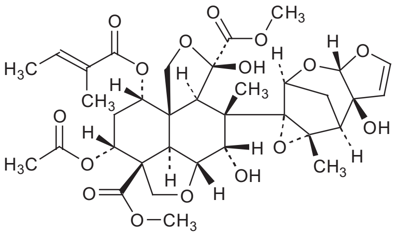
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Chemical assays

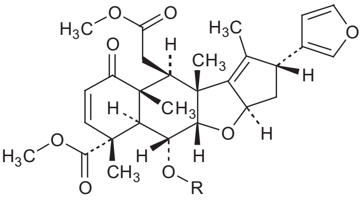
A high-performance liquid chromatography procedure is available for the quantitative determination of oxidized tetranortriterpenes (*16*).

Major chemical constituents

The major constituents are oxidized tetranortriterpenes including azadirachtin (azadirachtin A), azadiriadione, epoxyazadiradione, azadirone, nimbidin, nimbin, deacetylnimbin, salannin, gedunin, mahmoodin, 17-hydroxydiradione and related derivatives (*9, 11, 17–19*). The structures of azadirachtin, nimbin and deacetylnimbin are presented below:



azadirachtin



nimbin R = CO-CH_3

deacetylnimbin R = H

Medicinal uses

Uses supported by clinical data

As a contraceptive for intravaginal use (*20*), as a mosquito repellent (*21*), and for treatment of vaginal infections (*22*). However, further controlled clinical trials are needed before the oil can be recommended for general use.

Uses described in pharmacopoeias and well established documents

Treatment of gastric ulcers, cardiovascular disease, malaria, rheumatism and skin disorders. External applications for treatment of septic wounds, ulcers and boils (*7*).

Uses described in traditional medicine

Treatment of allergic skin reactions, asthma, bruises, colic, conjunctivitis, dysmenorrhoea, fever, gout, headache, itching due to varicella, kidney stones, leukorrhoea, psoriasis, scabies, sprains and muscular pain, and wounds (*10, 11*). As an emmenagogue, tonic, stomatic and vermicide (*9*).

Pharmacology

Experimental pharmacology

Antifertility activity

Oleum Azadirachti, 0.6 ml, was given to female rats by intragastric administration on days 8–10 of pregnancy, after confirming the presence

and number of embryo implants surgically on day 7. The animals were examined again under anaesthesia on day 15 of pregnancy to check the number of developing embryos. Controls received an equivalent regime of peanut oil. Complete resorption of embryos was observed on day 15 of pregnancy in every animal treated with Oleum Azadirachti while embryos were developing normally in controls (*23*). Intragastric administration of 6.0 ml of the oil per day for 60 days to female baboons induced abortion in pregnant animals (*24*).

A single intrauterine application of 100.0 µl of the oil produced a reversible block in fertility lasting for 107–180 days in female rats (*25*) and 7–11 months in monkeys (*26*). In an attempt to find an alternative to vasectomy for long-term male contraception, the effect of a single intra-vas application of the oil was assessed in male rats. Animals with proven fertility were given a single dose of 50.0 µl of the oil in the lumen of the vas deferens on each side. Control animals received the same volume of peanut oil. Animals were allowed free access to mating for 4 weeks after the treatment, with females of proven fertility. While the control animals impregnated their female partners, all males treated with Oleum Azadirachti remained infertile throughout the 8-month observation period. Epididymal and vas histologies were normal, with no inflammatory changes or obstruction. Intra-vas administration of the oil resulted in a block of spermatogenesis without affecting testosterone production. The seminiferous tubules, although reduced in diameter, appeared normal and contained mostly early spermatogenic cells. No anti-sperm antibodies were detected in the serum (*27*).

Subcutaneous administration of up to 0.3 ml of the oil to rats had no estrogenic, anti-estrogenic or progestational activity, and appeared not to interfere with the action of progesterone (*28*). Intravaginal application of 2.50 µl–0.25 ml of the oil to pregnant rats induced abortion (*29*).

The oil, 10–25%, inhibited fertilization in isolated mouse ova as assessed by sperm–egg interaction, and impaired the development of fertilized ova in vitro (*30*). In other investigations, the active constituents of the oil were identified to be a mixture of six compounds comprising saturated, mono and di-unsaturated free fatty acids and their methyl esters (*31*). The oil, 0.25–25.00 mg/ml, had spermicidal effects on human and rat sperm in vitro (*32, 33*).

Antihyperglycaemic activity

Intragastric administration of 21.0 mg/kg body weight (bw) of the oil reduced blood glucose levels in rats (*34*). A significant ($P < 0.01$) reduction in blood glucose levels was observed in normal and alloxan-induced dia-

betic rabbits after administration of 200.0 mg of the oil; the effect was more pronounced in diabetic animals (*35*).

Anti-inflammatory activity

The anti-inflammatory effects of nimbidin were assessed and compared with phenylbutazone. Intramuscular administration of 40.0 mg/kg bw of nimbidin reduced acute paw oedema in rats induced by carrageenan and kaolin. Formalin-induced arthritis in ankle joints and fluid exudation due to granuloma induced by croton oil in rats were also suppressed by similar treatment with the compound. In the acute phase of inflammation, nimbidin at 40.0 mg/kg bw was more active than phenylbutazone at 100.0 mg/kg bw (*36*). Intramuscular administration of 50.0 mg/kg bw of the oil reduced granuloma induced by cotton pellet in rats (*37*).

Antimicrobial and antiviral activity

The efficacy of a petroleum ether extract of the oil was investigated for its antimicrobial activity against certain bacteria and fungi and poliovirus, as compared with the oil. The extract had stronger antimicrobial activity than the oil and, in vitro at 2.0 mg/ml, inhibited the growth of *Escherichia coli* and *Klebsiella pneumoniae*, which were not inhibited by the oil. The extract was active against *Candida albicans* (minimum inhibitory concentration 0.25 mg/ml) and had antiviral activity against poliovirus replication in Vero African green monkey kidney cell lines at 50.0 µg/ml (*38*).

Intravenous administration of 60.0 mg/kg bw of the oil twice per day for 7 days protected mice from systemic candidiasis, as shown by enhanced survival and a reduction in colony-forming units of *C. albicans* in various tissues (*38*).

The oil inhibited the growth of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *S. pyogenes* in vitro at a concentration of 1.5–6.0% (*39*). A petroleum ether extract of the oil inhibited the growth of *Epidermophyton floccosum, Microsporum canis, M. gypseum, Trichophyton concentricum, T. rubrum* and *T. violaceum* (*40*).

Antiulcer activity

Intragastric administration of 40.0 mg/kg bw of nimbidin showed antiulcer activity in various experimental models (gastric lesions induced by acetylsalicylate, stress, serotonin and indometacin) in rats. The compound also protected against cysteamine- and histamine-induced duodenal lesions in rodents (*41*).

Estrogenic activity

Subcutaneous administration of 0.2–6.0 ml/kg bw of the oil to normal or ovariectomized rats had no estrogenic effects: there was no increase in uterine wet weight or disruption of the estrous cycle (*28, 29*).

Immune effects

Mice received Oleum Azadirachti, 150.0 µl/animal, or an emulsifying agent, with or without peanut oil, by intraperitoneal injection. Peritoneal lavage on subsequent days showed an increase in the number of leukocytic cells on day 3 following treatment with Oleum Azadirachti, and peritoneal macrophages exhibited enhanced phagocytic activity and expression of major histocompatability complex class II antigens. Treatment also induced the production of γ-interferon. The spleen cells of oil-treated animals showed a significantly higher lymphocyte proliferative response to in vitro challenge with concanavalin A or tetanus toxin than those of controls. Pretreatment with the oil did not augment the anti-tetanus-toxin antibody response. The results of this study indicate that the oil acts as a nonspecific immunostimulant and that it selectively activates cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge (*42*). Intraperitoneal administration of the oil to mice (150.0 µl/animal) and rats (120.0 µl/animal) enhanced phagocytosis of macrophages (*42, 43*).

Toxicology

Studies of the oral acute toxicity of the oil in rats and rabbits showed dose-related pharmacotoxic symptoms along with a number of biochemical and histopathological indices of toxicity. The 24-hour oral median lethal dose was 14.0 ml/kg bw in rats and 24.0 ml/kg bw in rabbits. Prior to death, all animals exhibited pharmacotoxic symptoms of a similar type and severity; the lungs and central nervous system were the target organs (*44*).

Intragastric administration of the oil to mice was not toxic at a dose of 2.0 ml. The oil (dose not specified) was nonirritant when applied to the skin of rabbits in a primary dermal irritation test. In a subacute dermal toxicity study, rabbits exposed to the oil (dose not specified) daily for 21 days showed no significant changes in body weight or organ:body weight ratio, serum oxaloacetic transaminase and pyruvic transaminase levels, and blood glucose and urea nitrogen values. No treatment-related histopathological changes were observed (*45*).

In a three-generation study carried out according to a World Health Organization/United States Food and Drug Administration protocol, groups of 15 male and 15 female rats were fed a diet containing 10% Oleum Azadirachti or peanut oil. Reproductive toxicology was monitored

for three generations. There were no adverse effects on the reproductive parameters in either group (*46*).

A group of 10 pregnant rats received 2.0 ml/kg bw of the oil by gastric administration daily and the animals were allowed to deliver at term. Six of the treated animals died between days 6 and 13 of pregnancy. Among the four remaining animals that delivered, one delivered a seemingly normal pup on day 27, but the pup died after 4 days. Autopsy performed on day 16 of pregnancy suggested that fetal resorption had occurred; however, no indication was given as to whether fetuses were normal (*47*).

Clinical pharmacology

Contraceptive activity

In an uncontrolled clinical trial involving 225 healthy fertile women aged 18–35 years performed to assess the efficacy of the oil as an antifertility agent, subjects were instructed to insert 1 ml of the oil into the vagina with a plastic applicator 5 minutes prior to coitus. No other contraception was used. After 16 months of use only three pregnancies due to drug failure were reported; there were 30 pregnancies due to noncompliance (i.e. in women who did not use the oil as instructed) (*20*).

Antibacterial activity

In a 2-week double-blind, placebo-controlled clinical trial involving 55 women with abnormal vaginal discharge due to bacterial vaginosis, subjects were instructed to insert 5.0 ml of the oil or placebo oil into the vagina daily. Treatment with the test oil was reported to cure the symptoms of the infection (*22*).

Insect repellent activity

In a field study carried out to evaluate the mosquito repellent action of the oil in villages in a forested area in Mandla District, Madhya Pradesh, India, various concentrations of the oil were mixed with coconut oil (1–4%) and applied to the exposed body parts of human volunteers. The mixture provided 81–91% protection from the bites of anopheline mosquitoes during a 12-hour period of observation (*21*).

Treatment of skin disorders

In one case report, administration of 100.0 mg of oil twice daily for 34 days completely healed chronic skin ulcers up to 1 cm deep (*48*).

Adverse reactions

A 60-year-old male was admitted to hospital with neurological and psychotic symptoms following ingestion of 60.0 ml of Oleum Azadirachti.

However, correlation of the adverse effects with ingestion of the oil was not definitely proven (*49*).

Contraindications

Oral administration of Oleum Azadirachti is contraindicated during pregnancy, nursing and in children under the age of 12 years.

Warnings

A number of cases of toxicity, including toxic encephalopathy, poisoning and Reye-like syndrome, following ingestion of excessive doses of Oleum Azadirachti have been reported (*50–52*).

Precautions

Drug interactions

Administration of the oil may reduce blood glucose levels. It should therefore be used with caution in insulin-dependent diabetic patients or patients taking oral antihyperglycaemic drugs.

Carcinogenesis, mutagenesis, impairment of fertility

An acetone extract of the oil was inactive at concentrations of up to 200.0 mg/plate in the *Salmonella*/microsome assay using *Salmonella typhimurium* strains TA98 and TA100 (*53*). In the same test, the oil (concentration not specified) was not mutagenic using *Salmonella typhimurium* strains TA98 and TA100, with or without metabolic activation (*54*).

The oil has demonstrated antifertility effects in numerous animal and human studies (see Pharmacology).

Pregnancy: teratogenic effects

The oil had embryotoxic effects after vaginal administration to pregnant rats at a dose of 0.25 ml/animal (*32*, *33*). Embryotoxic effects were also reported following intragastric administration of 4.0 ml/kg bw of the oil to pregnant rats on days 6–8 of pregnancy (*47*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions.

Dosage forms
Oil. Store in a tightly sealed container away from heat and light.

Posology
(Unless otherwise indicated)
Dose: 1.0–5.0 ml of oil for intravaginal applications (*20, 22*).

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Flos Carthami

Definition

Flos Carthami consists of the dried flowers of *Carthamus tinctorius* L. (Asteraceae) (*1–3*).

Synonyms

Asteraceae are also known as Compositae.

Selected vernacular names

American saffron, baharman, barre, bastard saffron, benibana, biri, centurakam, chôm pu, dok kham, dyer's saffron, esfer, fake saffron, false saffron, hong hoa, hong hua, hong-hua, honghua, huang hua, hung hua, hung-hua, Hungarian saffron, ik-kot, Indian safflower, kafishah, kajirah, karizeh, kazirah, kanar, kasube, kasubha, kasumba, kembang pulu, kham, kham foi, kham yong, khoinbo, kouranka, kusum, kusuma, kusumba, kusumphul, lago, qurtum, rum, saff-flower, safflower, saflor, safran bâtard, sáfrányos szeklice, saffron, saffron thistle, Saflor, senturakam, shawrina, sufir, usfur, wild saffron, za'afran (*3–8*).

Geographical distribution

Indigenous to the Arabian peninsula, north-west India and Islamic Republic of Iran; also found in the Mediterranean region of North Africa and in Cambodia, China, India, Indonesia, Lao People's Democratic Republic and Viet Nam. Widely cultivated around the world (*4, 6, 9–11*).

Description

An annual herb, 0.4–1.3 m high, much branched, glabrous, spiny. Branches stiff, cylindrical, whitish in colour. Leaves simple, spirally arranged, without petiole; oblong, ovate, lanceolate or elliptic; dark green, glossy, 3–15 cm long, 1.5 cm wide, spinous along the margin and at the tip. Flowers solitary, terminal, 2.5–4.0 cm in diameter with spreading outer leafy spiny bracts and inner triangular bracts, spine tipped, forming a conical involucre, with small opening at the tip. Florets, 30–90, tubular,

hermaphrodite, usually orange-yellow in colour; corolla tubes 4 cm long, with five pointed segments. Fruits white or grey, tetragonal achenes, about 8 mm long, without pappus (*6*).

Plant material of interest: dried flowers

General appearance

Red to red-brown corollas, yellow styles and stamens, rarely mixed with immature ovaries; corollas tubular, 1–2 cm long, with five segments; long pistils surrounded by five stamens; pollen grains yellow and spherical, approximately 50.0 µm in diameter, with fine protrusions on the surface (*1–3*).

Organoleptic properties

Odour: characteristic aromatic; taste: slightly bitter (*1–3*).

Microscopic characteristics

Information to be developed according to national requirements.

Powdered plant material

Orange-yellow with fragments of corolla, filament and stigma. Long tubular secretory cells, up to 66 µm in diameter, usually accompanied by vessels containing yellowish-brown to reddish-brown secretion. Outer walls of terminal epidermal cells of corolla lobes projecting to be tomentellate. Upper epidermal cells of stigma and style differentiated into conical unicellular hairs, acuminate or slightly obtuse at the apex. Pollen grains subrounded, elliptical or olivary, with three germinal pores, exine dentate spinose. Parenchymatous cells containing crystals of calcium oxalate, 2–6 µm in diameter (*3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), microchemical tests, spectrometry (*1–3*), and thin-layer chromatography (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Foreign organic matter

Not more than 2% (*1–3*).

Total ash
Not more than 18% (*1, 2*).

Loss on drying
Not more than 13% (*3*).

Pesticide residues
The recommended maximum limit for the sum of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

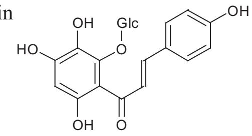
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

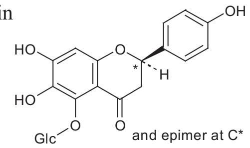
Chemical assays
To be established in accordance with national requirements. A high-performance liquid chromatography method for analysis of carthamin, safflor yellow A and other related pigments is available (*15*).

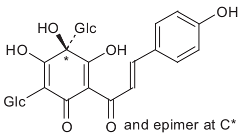
Major chemical constituents
The major constituent is the chalcone C-glucoside carthamin (up to 8.5%) (*16*). Other significant constituents include fatty acids, the chalcone hydroxysafflor yellow A; the nitrogenous chalcone tinctormine; the quinoid C-glycosides safflor yellow A and safflor yellow B; the flavonoids neocarthamin, quercetin, rutin, kaempferol and related hydroxy derivatives and glycosides; dotriacontane-6,8-diol, erythrohentriacontane-6,8-diol, heptacosane-8,10-diol, triacontane-6,8-diol and related alkanes (*8, 17, 18*). Representative structures of chalcones, quinoid C-glycosides and a flavanone are presented below.

carthamin

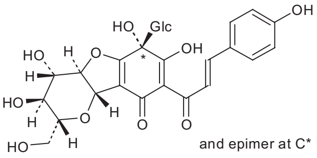


neocarthamin

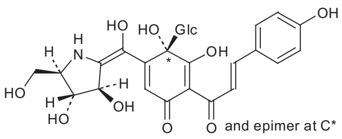




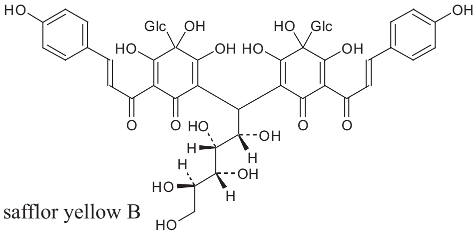
hydroxysafflor yellow A



safflor yellow A

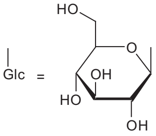


tinctormine



safflor yellow B

β-D-glucopyranosyl



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Treatment of amenorrhoea, dysmenorrhoea and wounds or sores with pain and swelling, and prevention of atherosclerosis (*3, 19*).

Uses described in traditional medicine

As an antipyretic, antidiarrhoeal, contraceptive, diaphoretic, emmenagogue, expectorant, laxative, sedative and stimulant (*8, 20, 21*). Treatment of bronchitis, boils, haemorrhoids, respiratory tract infections, ringworm and scabies (*8, 20*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 500.0 mg/kg body weight (bw) of a 95% ethanol extract of Flos Carthami reduced the responsiveness of mice as measured in the hot-plate test, indicating an analgesic effect, and also

decreased yeast-induced fevers (*22*). Subcutaneous administration of 10.0 g/kg bw of an aqueous extract of the flowers to mice did not reduce pain perception as measured in the hot-plate test (*23*). However, subcutaneous administration of 1.0–3.0 g/kg bw of a 50% methanol extract of the flowers to mice reduced writhing induced by acetic acid (*23*). Intragastric administration of 30.0 g/kg bw of a 50% methanol extract of the flowers to mice also reduced writhing induced by acetic acid (*24*).

Antihepatotoxic activity

Intraperitoneal injection of a methanol extract of 100.0 mg/kg bw of the flowers to rats reduced the increased activities of alkaline phosphatase, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase and lactate dehydrogenase, and reduced the plasma concentration of bilirubin in hepatotoxicity induced by the administration of α-naphthylisothiocyanate (*25*). However, intraperitoneal administration of 300.0 mg/kg bw of a methanol extract of the flowers to rats had no effect on hepatotoxicity induced by carbon tetrachloride (*26*). Conversely, administration of the flowers to rats prevented the development of liver cirrhosis induced by carbon tetrachloride in eight out of nine animals. In the control group, seven out of nine rats developed cirrhosis when treated with carbon tetrachloride (*27*).

Anti-inflammatory activity

Intragastric administration of 30.0 mg/kg bw of a 50% methanol extract of the flowers inhibited inflammation as measured by footpad oedema in mice, induced by carrageenan, serotonin, bradykinin, histamine or prostaglandin (*24*). Subcutaneous administration of 10.0 g/kg bw of an aqueous or 50% methanol extract of the flowers inhibited carrageenan-induced footpad oedema in mice (*23*).

In vitro, 1-butanol and petroleum ether extracts of the flowers had albumin-stabilizing effects, indicating anti-inflammatory activity; however, the aqueous extract was not active in this assay (*28*).

Antimicrobial activity

An ethanol extract of the flowers inhibited the growth of *Staphylococcus aureus* in vitro at a concentration of 0.5 mg/plate, but was not effective against *Escherichia coli* (*29*). A 95% ethanol extract of the flowers inhibited the growth of *Bacillus subtilis, Candida albicans, Salmonella typhosa* and *Staphylococcus aureus* in vitro at a concentration of 100.0 µg/plate, but was not effective against *E. coli* and *Shigella dysenteriae* (*30*). A hot aqueous extract of the flowers (concentration not specified) inhibited replication of poliomyelitis virus type 1 in vitro (*31*).

Cardiovascular effects

Intragastric administration of 4.0 g/kg bw of a 50% methanol extract of the flowers to male rats did not reduce congestive oedema induced by bilateral ligation of the jugular vein (*32*). Intravenous administration of 2.0 g/kg bw of a decoction of the flowers to dogs reduced ST-segment elevation and the increased heart rate induced by occlusion of the apical branch of the coronary artery (*33*). Intraperitoneal administration of a hot aqueous extract of 10.0 g/kg bw of the flowers to gerbils reduced ischaemia and neurological damage induced by unilateral carotid artery ligation when compared with untreated animals (*34*). In vitro, an aqueous extract of the flowers (concentration not specified) displayed calcium-channel blocking activity by displacing nitrendipine or diltiazem from receptor sites (*35*). Tinctormine (concentration not specified) isolated from the flowers, also showed in vitro calcium antagonist activity (*17*).

A 95% ethanol extract of the flowers (dose not specified) induced vasodilation in guinea-pigs and rabbits (*36*). Safflower yellow (containing chalconoid compounds of which 75% is safflomin A) extracted from the flowers (dose not specified) lowered blood pressure in spontaneously hypertensive rats; 5 weeks later, the plasma renin activity and angiotensin II levels were reduced in these animals, suggesting that the reduction in blood pressure was mediated by the renin-angiotensin system (*37*). An aqueous extract of the flowers, 10.0 µg/ml, inhibited the activity of stress-activated protein kinases from isolated ischaemic rat hearts by 50%; when the isolated hearts were treated prior to the induction of ischaemia, the inhibition was 95% (*38*).

Central nervous system depressant activity

Subcutaneous administration of 1.0–10.0 g/kg bw of an aqueous or 50% methanol extract of the flowers had central nervous system depressant effects in mice and relaxed skeletal muscles (*23*). Intraperitoneal administration of 500.0 mg/kg bw of a methanol extract of the flowers per day for 3 days did not potentiate barbiturate-induced sleeping time in mice (*39*). Subcutaneous administration of 10.0 g/kg bw of a 50% methanol extract of the flowers inhibited pentylenetetrazole-induced convulsions in mice (*23*).

Immune system effects

Intraperitoneal administration of 50.0–450.0 mg/kg bw of safflower yellow extracted from the flowers per day for 6 days suppressed antibody formation in mice (*40*). Intraperitoneal administration of 50.0 mg of an aqueous extract of the flowers per day for 6 days to mice delayed cutaneous hypersensitivity reactions, demonstrating immune suppressant activ-

ity. Administration of the extract resulted in decreased lysozyme concentrations, decreased phagocytosis of macrophages and leukocytes, and diminished production of plaque-forming cells, rosette-forming cells, and antibodies. The extract also delayed the responsiveness and activation of T-suppressor lymphocytes (*40*).

Platelet aggregation inhibition

Intraperitoneal administration of 30.0 mg of an aqueous extract of the flowers to mice reduced platelet aggregation induced by adenosine diphosphate (ADP) by 65% in γ-irradiated animals (*41*). Intraperitoneal administration of 0.1 g/kg bw of an ethyl acetate or aqueous extract of the flowers to mice had no effects on platelet aggregation (*42*).

An aqueous extract of the flowers, 2.27 mg/ml, inhibited ADP-induced platelet aggregation by 24.7% in platelets isolated from irradiated rabbits (*41*). Aqueous, hexane and 90% ethanol extracts of the flowers, 5.0 mg/ml, inhibited platelet aggregation induced by ADP, arachidonic acid and collagen in rat platelets (*43*).

Uterine stimulant effects

Intraperitoneal administration of a hot aqueous extract of the flowers (dose not specified) increased uterine contractions in pregnant female rats (*31*).

Toxicology

Intragastric or subcutaneous administration of 10.0 g/kg bw of a 50% ethanol extract of the flowers to mice had no toxic effects (*44*). The intraperitoneal median lethal dose (LD_{50}) of a decoction of the flowers in mice was 1.2 g/kg bw (*19*). The intravenous LD_{50} of a 50% ethanol extract of the flowers in mice was 5.3 g/kg bw. The intravenous and oral LD_{50} values of carthamin in mice were 2.35 g/kg bw and > 8.0 g/kg, respectively. No toxic effects or death of animals was reported after intraperitoneal administration of 12.5 g/kg of a decoction of the flowers per day for 2 days to mice. Chronic administration of 0.015–1.5 g/kg bw of carthamin in the diet per day for 3 months had no toxic effects on the heart, liver, kidneys or gastrointestinal tract of young rats (*19*).

Clinical pharmacology

No information available.

Adverse reactions

Increased menstrual flow may occur (*19*). Dizziness, skin eruptions and transient urticaria have been reported (*19*).

Contraindications

Owing to its traditional use as an emmenagogue and its stimulatory effects on the uterus, Flos Carthami should not be administered during pregnancy. Flos Carthami is also contraindicated in haemorrhagic diseases, peptic ulcers and excessive menstruation (*19*).

Warnings

No information available.

Precautions

Drug interactions

Although no drug interactions have been reported, extracts of Flos Carthami inhibit platelet aggregation (*41, 43*). The flowers should therefore be used with caution in patients taking anticoagulants or antiplatelet drugs.

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous or methanol extract of the flowers was not mutagenic in concentrations up to 100.0 mg/ml in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation with liver microsomes (*45, 46*). An aqueous or methanol extract of the flowers, 100.0 mg/ml, was not mutagenic in the *Bacillus subtilis* recombination assay (*45*). However, other investigators have reported that aqueous extracts of the flowers were mutagenic at concentrations of 50.0 µg/ml and 5.0 mg/plate in *S. typhimurium* strains TA98 and TA100 (*29, 47*). Intraperitoneal administration of 4.0 g/kg bw of an aqueous extract of the flowers to mice was mutagenic (*46*).

Intragastric administration of 240 mg of an aqueous extract of the flowers to female rats had no effects on fetal implantation and no embryotoxic effects (*8*). Intragastric administration of 2.0 g/kg bw of an aqueous extract of the flowers twice per day to female rats throughout pregnancy had no effect on implantation, gestation or duration of fetal expulsion, but did cause fetal loss by resorption (*48*).

Pregnancy: teratogenic effects

Pregnant mice were treated with varying doses of an aqueous extract of the flowers during days 0–8 of gestation, and the embryos were isolated and evaluated on day 13 of the gestational period. The results showed that, at doses of 1.6 mg/kg bw and 2.0 mg/kg bw per day, the extract induced embryo absorption, while at 1.2 mg/kg bw per day, changes in the

external, internal and longitudinal diameters, open neuropore, cellular orientation and cellular degeneration were observed (*49*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
No information available. However, owing to possible mutagenic effects, use of Flos Carthami during nursing should be only on the advice of a health-care professional.

Paediatric use
No information available. However, owing to possible mutagenic effects, use of Flos Carthami in children should be only on the advice of a health-care professional.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions.

Dosage forms

Dried flowers for infusions and decoctions; extracts. Store in a cool dry place protected from moisture (*3*).

Posology

(Unless otherwise indicated)
Average daily dose: 3.0–9.0 g of Flos Carthami as an infusion or decoction; equivalent for other preparations (*2, 3*).

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Stigma Croci

Definition

Stigma Croci consists of the dried stigmas of *Crocus sativus* L. (Iridaceae) (*1, 2*).

Synonyms

Crocus officinalis Martyn (*3*).

Selected vernacular names

Açcfrão, azaferan, azafran, crocus, crocus hispanicus, crocus orientalis, dye saffron, Echter Safran, fan-hung-hua, Gewürzsafran, hay saffron, kamkana, kesar, keshara, koema-koema, kumkum, Safran, saffraon, saffron, saffron crocus, sáfrány, sapran, Spanish saffron, true saffron, szafran, szafrana, z'afaran, za afran l-hor, zaafaran, zafaran, zafarfon, zafferano, zang hong hua, zafrane hor (*1–6*).

Geographical distribution

Indigenous to southern Europe and south-western Asia. Cultivated in the Eastern Mediterranean and in China, France, India, Italy and Spain (*4, 5*).

Description

A perennial, low growing (8–30 cm high), bulbous herb with an underground globular corm, producing six to nine sessile leaves, surrounded in its lower part by four or five broad membranous scales. Flowers borne on the terminal region of a scape, each flower consisting of a pale reddish-purple perianth showing a cylindrical tube about 10 cm long and six oblong oval segments, an androecium of three stamens and a gynoecium of three syncarpous carpels. Ovary inferior, three-locular. Style slender, elongated and pale yellow in the perianth tube, divided in its upper part into three drooping, deep-red stigmas (*4, 7*).

Plant material of interest: dried stigmas

General appearance

Thin cord-like stigmas, dark yellow-red to red-brown, 1.5–3.5 cm long, tripartite or separate, the upper part broader and slightly flattened, the distal end split longitudinally and rolled into a slender funnel with a crenate edge. Margin of the apex irregularly dentate, with a short slit at the inner side, sometimes with a small piece of style remaining at the lower end. Texture light, lax and soft, without oily lustre (*1, 2, 8*).

Organoleptic properties

Odour: characteristic, aromatic, slightly irritant; taste: pungent, slightly bitter (*1, 2, 8*).

Microscopic characteristics

When softened by immersion in water, upper ends of the stigmas show numerous tubular protrusions about 150 µm long, with a small number of pollen grains, which are spherical, smooth and without spines (*1, 9, 10*).

Powdered plant material

Orange-red. Epidermal cells long, thin-walled, slightly sinuous, stripe-shaped in the surface view; outer walls sometimes protrude, showing papillae, with indistinct fine striations. Terminal epidermal cells of stigma are papillose, 26–56 µm in diameter, with sparse striations on the surface. Parenchymatous cells are crowded with round-fascicle, fusiform or subsquare granular crystals of calcium oxalate, 2–14 µm in diameter (*2*).

General identity tests

Macroscopic and microscopic examinations, microchemical and spectrophotometric tests (*1, 2*), and thin-layer chromatography (*11*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Total ash

Not more than 7.5% (*1, 2*).

Loss on drying

Not more than 12.0% (*1, 2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

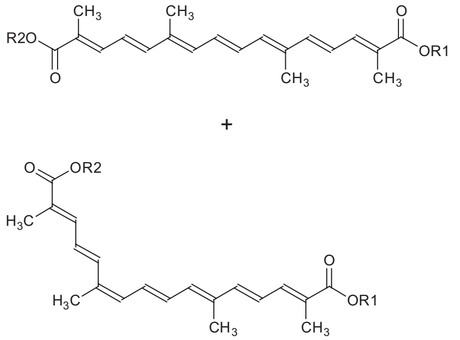
Other purity tests
Chemical, foreign organic matter, acid-insoluble ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Colorimetric (*1*) and spectrophotometric (*2*) assays are used. Qualitative and quantitative high-performance liquid chromatography methods are available for picrocrocin, safranal and crocins (*15–17*).

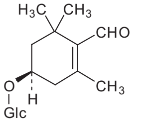
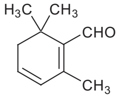
Major chemical constituents
The major constituents include essential oils (0.4–1.3%) with α- and β-pinene, 1,8-cineole (eucalyptol), a monoterpene glucoside, picrocrocin (4%), safranal, which can be obtained by hydrolysis of picrocrocin, and a series of carotenoid glucosides known as crocins (2%), dimethylcrocetin and their aglycone crocetin (*3, 8*). Representative structures are presented below.

Medicinal uses
Uses supported by clinical data
None. Although Stigma Croci showed antioxidant effects in human studies (*18*), data from controlled clinical trials are lacking.

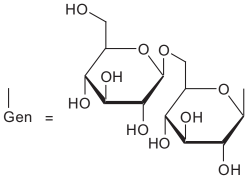
Uses described in pharmacopoeias and well established documents
As a tonic and antiarteriosclerotic (*19, 20*), and as a sedative and emmenagogue (*2, 5, 21*).

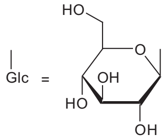


	R1	R2
α-crocetin (crocetin)	H	H
β-crocetin	H	CH_3
and	CH_3	H
γ-crocetin (dimethylcrocetin)	CH_3	CH_3
A-crocin (crocin)	Gen	Gen
B-crocin (crocin 2)	Gen	Glc
and	Glc	Gen
C-crocin (crocin 3)	Gen	H
and	H	Gen
D-crocin (crocin 4)	Glc	Glc
E-crocin	Glc	H
and	H	Glc

picrocrocin  safranal 

gentiobiosyl :

6–O–β-D-glucopyranosyl-β-D-glucopyranosyl 

β-D-glucopyranosyl 

Uses described in traditional medicine

As an emmenagogue and for treatment of ammenorrhoea, abdominal pain, coughs, depression, digestive ailments, fever and pain due to wounds (*22, 23*). Also as an aphrodisiac, appetite stimulant, diaphoretic, contraceptive, antispasmodic and nerve sedative (*6, 22*).

Pharmacology

Experimental pharmacology

Antiarteriosclerotic effects

Administration of a monthly intramuscular injection of crocetin (dose not specified) to rabbits fed an atherosclerosis-inducing diet reduced serum cholesterol concentrations by 50%, and reduced the severity of atherosclerosis by ~30% (*24*).

Anticoagulant activity

A hot aqueous extract of Stigma Croci, 10–100.0 mg/ml, prolonged partial thromboplastin and prothrombin times, and inhibited platelet aggregation in human platelets induced by adenosine diphosphate and collagen in vitro (*25*).

Cell proliferation inhibition

Treatment of cervical epitheloid carcinoma (HeLa) cells with a concentrated extract (undefined) of the stigmas, 50.0–150.0 µg/ml, for 3 hours

inhibited colony formation by 25% and decreased the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) by 50% in vitro (*26, 27*).

Crocin and crocetin, 0.8–2.0 µmol/l, isolated from an extract of the stigmas, inhibited the growth of human acute promyelocytic leukaemia cells in vitro (*28*). Crocetin, 35–55.0 µg/ml, inhibited the synthesis of nucleic acids and protein in cervical epitheloid carcinoma, lung carcinoma and transformed fetal fibroblast malignant human cell lines (*29*). Incubation of cervical epitheloid carcinoma cells (HeLa), lung adenocarcinoma cells (A549) and SV-40 transformed fetal lung fibroblast cells with varying concentrations of crocetin for 3 hours resulted in a dose-dependent reduction in DNA and RNA synthesis, and suppression of RNA polymerase II activity (*26*).

Central nervous system effects

Intragastric administration of 125–250.0 mg/kg body weight (bw) of a 50% ethanol extract of the stigmas had a tranquillizing effect in mice, and potentiated the sedative effects of barbiturates (*30*).

Chemical carcinogenesis inhibition

Topical application of 100 mg/kg bw of a 95% ethanol extract of the stigmas inhibited two-stage initiation and promotion of skin carcinogenesis in mice, delaying the onset of papilloma formation and reducing the mean number of papillomas per mouse (*31*). Intragastric administration of 100.0 mg/kg bw of the same extract per day for 30 days reduced the incidence of soft tissue sarcomas induced by 20-methylcholanthrene by 10% in mice (*31*). Intragastric administration of 100.0 mg/kg bw of an ethanol extract of the stigmas to mice inhibited the growth of solid Dalton lymphoma ascites and sarcoma 180 tumours by 87% and 41%, respectively (*23, 32*). Subcutaneous administration of 400.0 mg/kg bw of crocin weekly for 13 weeks, slowed the growth of colon adenocarcinoma and increased the lifespan of female but not male mice (*33*).

Intraperitoneal administration of 50 mg/kg bw of a 95% ethanol extract of the stigmas to mice partially prevented the decreases in body weight, haemoglobin levels and leukocyte counts caused by cisplatin treatments (*32*).

Circulation effects

External application of a 1% aqueous solution containing crocin analogues isolated from *Crocus sativus* significantly ($P < 0.05$) increased blood flow to the retina and choroid in rabbits with ocular hypertension. Intraperitoneal administration of 10.0 mg/kg bw of crocin analogues to rats facili-

tated the recovery of retinal function after induction of retinal ischaemia by occlusion of the central retinal and posterior ciliary arteries (*34*).

Cytotoxicity
In vitro, crocin had potent cytotoxic effects on human and animal adenocarcinoma cells, with median lethal doses (LD_{50}) of 0.4 mmol/l and 1.0 mmol/l, respectively (*33*). An aqueous extract of the stigmas (LD_{50} 2.3 mg/ml), crocin (LD_{50} 3 mmol/l), picrocrocin (LD_{50} 3 mmol/l) and safranal (LD_{50} 0.8 mmol/l) inhibited the growth of HeLa cells in vitro. The cells treated with crocin exhibited wide cytoplasmic vacuole-like areas, reduced cytoplasm and cell shrinkage, indicating the induction of apoptosis (*35*).

Nootropic effects
An unspecified alcohol extract of the stigmas enhanced learning and memory in learning-impaired mice (*36*). Intragastric administration of 125.0–500.0 mg/kg bw of the extract did not affect learning behaviours in normal mice, but prevented ethanol-induced learning impairment, and prevented ethanol-induced inhibition of hippocampal long-term potentiation (a form of activity-dependent synaptic plasticity that may support learning and memory) in anaesthetized rats (*30, 36*). Intragastric administration of a single dose of 250.0 mg/kg bw of the same extract prevented acetaldehyde-induced inhibition of long-term potentiation in the dentate gyrus of anaesthetized rats (*37*). In a follow-up study, treatment of mice with an ethanol extract of 250.0 mg/kg bw of the stigmas improved ethanol-induced impairments of learning behaviours in mice and prevented ethanol-induced inhibition of hippocampal long-term potentiation (*38*). The effect was attributed to crocin, but not crocetin.

Toxicity
The LD_{50} for Stigma Croci was reported to be 20.7 g/kg bw in rodents (*23*). The LD_{50} of a 95% ethanol extract of the stigmas was > 600 mg/kg bw in mice (*39*). Mice treated with dimethylcrocetin isolated from the stigmas did not exhibit haematological or biochemical toxic effects after intragastric administration of up to 50.0 mg/kg bw (*23*).

Clinical pharmacology
The antioxidant effects of the stigmas were assessed in a clinical trial involving 30 subjects in three groups: 10 healthy volunteers, 10 patients with coronary artery disease and 10 healthy controls. The two test groups received 50 mg of Stigma Croci in 100.0 ml of milk twice daily for 6 weeks, the controls received milk only. Lipoprotein oxidation in blood samples

decreased by 42.3% in healthy volunteers ($P < 0.001$) and 37.9% ($P < 0.01$) in patients with coronary artery disease compared with controls (*18*).

Adverse reactions

The lethal dose of Stigma Croci is reported to be 20.0 g; however, smaller doses may cause vomiting, uterine bleeding, bloody diarrhoea, haematuria, bleeding from the nose, lips and eyelids, vertigo, numbness and yellowing of the skin and mucous membranes (*5*). Oral administration of 5.0 g resulted in localized skin haemorrhages, marked thrombocytopenia, and abnormalities of blood clotting in one patient (*40*).

Contraindications

Stigma Croci may induce uterine contractions and is therefore contraindicated during pregnancy (*5*). Owing to a lack of safety data, use of the stigmas in children and nursing mothers should be restricted to normal food use. Stigma Croci is contraindicated in bleeding disorders.

Warnings

At doses of 5.0 g or more, Stigma Croci may cause serious adverse reactions (see Adverse reactions). Overdose of Stigma Croci (12.0–20.0 g/day) may be fatal (*7, 22*).

Precautions

Drug interactions

Stigma Croci inhibits platelet aggregation and should therefore be used with caution in patients taking anticoagulant or antiplatelet drugs.

Carcinogenesis, mutagenesis, impairment of fertility

Ethyl acetate, methanol and aqueous extracts of Stigma Croci (concentrations not specified) were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation (*41*). Crocin and dimethylcrocetin,1.0 mg/plate, 2.0 mg/plate and 4.0 mg/plate, were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strain TA 1535 (*23*). A chloroform-methanol extract (2:1) of the stigmas, 100.0 mg/plate, was not mutagenic in pig kidney cells or in trophoblastic placenta cells (*42*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms
Dried stigmas; extracts of dried stigmas. Store the dried stigmas in a tightly sealed metal or glass container, protected from light and moisture (*5*).

Posology
There is insufficient information available to give an accurate assessment of dose range. No risk is associated with consumption in standard food use quantities (*22, 43*). The recommended therapeutic daily dose is 3.0–9.0 g (*2*). However, owing to a report of toxicity at 5.0 g (*40*), doses below 5.0 g/day are recommended.

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Fructus Foeniculi

Definition

Fructus Foeniculi consists of the dried ripe fruits of *Foeniculum vulgare* Mill. (Apiaceae) (*1–8*).[1]

Synonyms

Anethum foeniculum Clairv., *A. foeniculum* L., *A. rupestre* Salisb., *Feniculum commune* Bubani, *Foeniculum azoricum* Mill., *F. capillaceum* Gilib., *F. dulce* DC., *F. foeniculum* (L.) H. Karst., *F. officinale* All., *F. panmorium* DC., *F. piperitum* DC., *F. sativum* Bertol, *Ligusticum divaricatum* Hoffmannsegg et Link, *L. foeniculum* Crantz, *Meum foeniculum* (L.) Spreng., *Ozodia foeniculacea* Wight et Arn., *Selinum foeniculum* (L.) E.H.L. Krause (*2, 3, 9, 10*). Apiaceae are also known as Umbelliferae.

Selected vernacular names

Aneth doux, arap saçi, besbes, bitter fennel, Bitterfenchel, brotanis, common fennel, dill, édeskömény, erva doce, fãnksal, fannel, Fencel, Fenchel, fenchul, Fennekel, fennel, Fennichl, fennikel, Fennkol, fenouil, fenucchiello, fenucchio, fenykl, finkel, Finkel, finichio, finocchio, finucco, fiolho, florence fennel, foenoli doux, funcho, gemeiner Fenchel, Gemüsefenchel, giant fennel, guvamuri, hierba de anis, hinojo, hui-hsiang, imboziso, insilal, koper wloski, lady's chewing tobacco, large fennel, madesi souf, madhurika, marathoron, maratrum, marui, misi, nafa, panmauri, razianeh, razianaj, sanuf, shamar, shomar, sladkij ukrop, sohoehyang, sopu, spingel, sup, thian khaao phlueak, thian klaep, venkel, sweet fennel, uikyo, uikyou, vegetable fennel, vinkel, wild fennel, xiao hui, xiaohuixiang, yi-ra (*2, 3, 6, 8, 9, 11–14*).

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[1] The *European pharmacopoeia* (*7*) recognizes *Foeniculum vulgare* Mill. ssp. *vulgare* var. *vulgare* (Foeniculi amari fructus, Bitter Fennel) and *F. vulgare* Mill. ssp. *vulgare* var. *dulce* (Foeniculum dulcis fructus, Sweet Fennel) as distinct entities for which separate monographs are provided. However, in the biological literature, a clear delineation at the variety level is generally not made. Therefore, this monograph has not made the distinction between the "bitter" and "sweet" varieties.

Geographical distribution

Indigenous to the Mediterranean region. Cultivated in Europe, Asia and temperate regions of Africa and South America (*2, 12, 15*).

Description

Perennial aromatic herb, 1–3 m high with green, glaucous, furrowed, branched stems bearing alternate leaves, 2–5 times pinnate with extremely narrow leaflets. Superior leaves with sheaths longer than the blade. Umbels compound, large, nearly regular, on long peduncles. Flowers yellow, no involucre; calyx with five very slight teeth; petals five, entire, tips involute; stamens five; ovary two-celled; stylopodium large, conical. Fruit an oblong cremocarp, 6–10 mm long, 1–4 mm in diameter, greenish; glabrous mericarp compressed dorsally, semicylindrical, with five prominent, nearly regular ribs. Seeds somewhat concave, with longitudinal furrows (*3, 15, 16*).

Plant material of interest: dried ripe fruits

General appearance

Cremocarp, oblong 3.5–10.0 mm long, 1–3 mm wide, externally greyish yellow-green to greyish yellow often with pedicel 2–10 mm long. Mericarps usually free, glabrous, each bearing five prominent slightly crenated ridges (*1–4, 7, 8*).

Organoleptic properties

Odour: characteristic, aromatic; taste: sweet to bitter (*1–4, 8*).

Microscopic characteristics

Outer epidermis of the pericarp consists of thick-walled, rectangular, polygonal, colourless cells, with smooth cuticle, few stomata and no hairs. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, appearing elliptical in section and possessing brown epithelial cells; traversed in the ridges by vascular bundles, each having one inner xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres; some of the mesocarp cells, especially those about the vascular bundles, possess lignified, reticulate cells. Endocarp composed of one layer of flattened thin-walled cells varying in length, but mostly 4–6 µm thick, arranged parallel to one another in groups of five to seven. Endosperm, formed of somewhat thick-walled polygonal cellulosic parenchyma containing fixed oil, several aleurone grains (up to 6 µm in diameter) enclosing a globoid, and one or more microrosette crys-

tals of calcium oxalate, about 3 µm in diameter. Carpophore often not split, with thick-walled sclerenchyma in two strands (*2, 8*).

Powdered plant material

Greyish-brown to greyish-yellow. Yellowish-brown-walled polygonal secretory cells, frequently associated with a layer of thin-walled transversely elongated cells 2–9 µm wide, in a parquet arrangement; reticulate parenchyma of the mesocarp; numerous fibre bundles from the ridges, often accompanied by narrow spiral vessels; very numerous endosperm fragments containing aleurone grains, very small microrosette crystals of calcium oxalate, and fibre bundles from the carpophore (*7*).

General identity tests

Macroscopic and microscopic examinations (*1–4, 7, 8*), thin-layer chromatography for the presence of anethole and fenchone (7), and gas chromatography for the presence of anethole, fenchone and estragole (*7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*17*).

Foreign organic matter

Not more than 1.5% peduncles and not more than 1.5% other foreign matter (*4, 7*).

Total ash

Not more than 10% (*1, 4, 7, 8, 18*).

Acid-insoluble ash

Not more than 1.5% (*1, 2, 4*).

Water-soluble extractive

Not less than 20% (*3*).

Alcohol-soluble extractive

Not less than 11% (*3*).

Moisture

Not more than 8% (*7*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*19*). For other pesticides, see the *European pharmacopoeia* (*19*) and the WHO guidelines on quality control methods for medicinal plants (*17*) and pesticide residues (*20*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*17*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*17*) for the analysis of radioactive isotopes.

Other purity tests

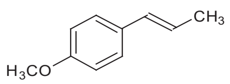
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

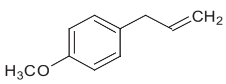
Contains not less than 1.4% v/w essential oil (*1, 2, 4, 6*).

Major chemical constituents

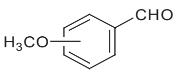
The major constituent is the essential oil (2–6%), which contains *trans*-anethole (50–82%), (+)-fenchone (6–27%), estragole (methylchavicol) (3–20%), limonene (2–13%), *p*-anisaldehyde (6–27%), α-pinene (1–5%) and α-phellandrene (0.1–19.8%) (*9, 12, 14, 21, 22*). Representative structures are presented below.



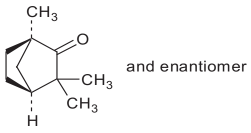
trans-anethole



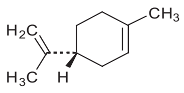
estragole



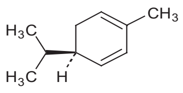
anisaldehyde



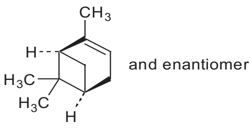
fenchone



(+)-limonene



(-)-α-phellandrene



α-pinene

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents
Symptomatic treatment of dyspepsia, bloating and flatulence (*9, 23–25*). As an expectorant for mild inflammation of the upper respiratory tract (*24, 26*). Treatment of pain in scrotal hernia, and dysmenorrhoea (*8*).

Uses described in traditional medicine
Treatment of blepharitis, bronchitis, constipation, conjunctivitis, diabetes, diarrhoea, dyspnoea, fever, gastritis, headache, pain, poor appetite and respiratory and urinary tract infections (*14*). As an aphrodisiac, anthelminthic, emmenagogue, galactagogue and vermicide (*14, 27, 28*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 500 mg/kg body weight (bw) of a 95% ethanol extract of Fructus Foeniculi to mice reduced the perception of pain as measured in the hot-plate test, and decreased yeast-induced pyrexia (*29*). Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats had significant ($P < 0.05$) analgesic activity in the hot-plate reaction test (*30*). In mice with yeast-induced pyrexia, treatment with 500.0 mg/kg bw of the same extract reduced rectal temperature from 36.5 °C to 34.7 °C 90 minutes after administration (*30*).

Antimicrobial activity

An essential oil from the fruits inhibited the growth of *Alternaria* species, *Aspergillus flavus, A. nidulans, A. niger, Cladosporium herbarum, Cunninghamella echinulata, Helminthosporium saccharii, Microsporum gypseum, Mucor mucedo, Penicillium digitatum, Rhizopus nigricans, Trichophyton roseum* and *T. rubrum* in vitro (*31, 32*). In another study, an essential oil was not active against *Aspergillus* species in vitro but a methanol extract of the fruits inhibited the growth of *Helicobacter pylori* (the bacterium associated with gastritis and peptic ulcer disease) in vitro, minimum inhibitory concentration 50.0 µg/ml (*33*). An essential oil from the fruits inhibited the growth of *Candida albicans, Escherichia coli, Lentinus lepideus, Lenzites trabea, Polyporus versicolor, Pseudomonas aeruginosa* and *Staphylococcus aureus* (*34*), and *Kloeckera apiculata, Rhodotorula rubra* and *Torulopsis glabrata* (*35*) in vitro. An ethyl acetate extract of the seeds inhibited the growth of *Shigella flexneri* (*36*), and an 80% ethanol extract of the seeds inhibited the growth of *Bacillus subtilis* and *Salmonella typhi* at concentrations of 250.0 µg/ml in vitro (*37*).

Antispasmodic activity

An ethanol extract of the fruits, 2.5–10.0 ml/l, 1 part fruits:3.5 parts 31% ethanol, inhibited acetylcholine- and histamine-induced guinea-pig ileal contractions in vitro (*23*). An essential oil from the fruits reduced intestinal spasms in mouse intestine, and was 26% as active as papaverine (*38*). Intragastric administration of 2.0–3.0 g/kg bw of an infusion of the fruits to cats inhibited acetylcholine- and histamine-induced ileum spasms by 50% (*39*). An essential oil from the fruits, 25.0 µg/ml and 10.0 µg/ml, respectively, inhibited oxytocin- and prostaglandin E_2-induced contractions of isolated rat uterus and reduced the frequency of the latter but not the former (*40*).

Cardiovascular effects

Intravenous administration of a 50% ethanol extract of the fruits (dose not specified) reduced blood pressure in dogs (*41*). An aqueous extract of the fruits, 10% in the diet, reduced blood pressure in rats. The effect was abolished by pretreatment of the animals with atropine (*42*). An unspecified extract of the seeds had diuretic effects in rabbits after intragastric administration. The effect was blocked by pretreatment of the animals with morphine (*43*).

Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats induced diuresis. The effect was comparable to that observed in animals treated with 960.0 mg/kg bw of urea, and was almost double that in controls (*30*).

Estrogenic and antiandrogenic activities

Intragastric administration of 2.5 mg/kg bw of an acetone extract of the seeds daily for 15 days to male rats decreased the protein concentration in the testes and vas deferens, and increased it in the seminal vesicles and prostate gland (*44*). The same dose of the same extract administered to female rats daily for 10 days increased the weight of the mammary glands, while higher doses induced vaginal cornification, increased the weight of the oviduct, endometrium, myometrium, cervix and vagina, and induced estrus (*44*). A follow-up study demonstrated that the acetone extract induced cellular growth and proliferation of the endometrium, and stimulated metabolic changes in the myometrium of rats. These changes appeared to favour the survival of spermatocytes and the implantation of the zygote in the uterus (*45*). Conversely, intragastric administration of 2.0 g/kg bw of an aqueous extract of the seeds per day for 25 days significantly ($P < 0.025$) reduced female fertility in mice compared with controls. No effect was observed in male mice (*46*).

Intragastric administration of 0.5 mg/kg bw or 2.5 mg/kg bw of an acetone extract of the fruits per day for 10 days to ovariectomized female rats had estrogenic effects (*45*). Intragastric administration (dose not specified) of an essential oil from the fruits to goats increased the amount of milk produced and the fat content of the milk (*47*). Lactating mice fed the fruits in the diet (concentration not specified) produced pups that ate a larger quantity of fennel-containing foods, suggesting that the constituents of the fruits may be passed in breast milk (*48*). Intragastric administration of 250.0 mg/kg bw of unspecified extracts of the fruits induced estrus and increased the size of the mammary glands and oviducts in adult ovariectomized rats, and exerted an antiandrogenic effect in adult male mice. It also increased the weight of the cervix and vagina of ovariectomized rats, and increased the concentration of nucleic acids and protein in cervical and vaginal tissues. The hyperplasia and hypertrophy of the cervix and vagina were similar to changes seen during estrus in normal female rats (*45*).

Subcutaneous administration of anethole (dose not specified) to sexually immature female rats increased uterine weight and induced estrus. However, in ovariectomized mice the same treatment was not estrogenic (*49*). Intramuscular injection of 100.0 mg/kg bw or 500.0 mg/kg bw of anethole per day for 7 days to rats induced a significant decrease in dorsolateral prostate weight ($P < 0.05$) (*50*). Intragastric administration of 50.0 mg/kg bw, 70.0 mg/kg bw or 80.0 mg/kg bw of *trans*-anethole to rats had anti-implantation effects, with the maximum effect (100%) at the highest dose (*51*). The compound showed estrogenic effects, and did not demonstrate anti-estrogenic, progestational or androgenic effects (*51*).

Expectorant and secretolytic effects

Application of an infusion of Fructus Foeniculi, 9.14 mg/ml, to isolated ciliated frog oesophagus epithelium increased the transport velocity of fluid by 12%, suggesting an expectorant effect (*52*). Administration of 1.0–9.0 mg/kg bw anethole and 1.0–27.0 mg/kg bw fenchone by inhalation to urethanized rabbits produced a decrease in the specific gravity of the respiratory fluid and enhanced the volume output of respiratory tract fluid (*53*).

Gastrointestinal effects

Intragastric administration of 24.0 mg/kg bw of the fruits increased spontaneous gastric motility in unanaesthetized rabbits; at a dose of 25.0 mg/kg bw the fruits reversed the reduction of gastric motility induced by pentobarbital (*54*).

Sedative effects

Intragastric administration of an essential oil from the fruits (dose not specified) to mice reduced locomotor activity and induced sedation (*55*). A single intraperitoneal administration of 200.0 mg/kg bw of an ether extract of the seeds enhanced barbiturate induced sleeping time in mice. However, intragastric administration of 200.0 mg/kg bw of the extract per day for 7 days decreased barbiturate-induced sleeping time (*56*).

Toxicology

Intragastric administration of 3.0 g/kg bw of a 95% ethanol extract of the fruits induced piloerection and reduced locomotor activity in mice (*30*). Acute (24-hour) and chronic (90-day) oral toxicity studies with an ethanol extract of the fruits were performed in rodents. Acute doses were 0.5 g/kg, 1.0 g/kg and 3.0 g/kg per day; the chronic dose was 100.0 mg/kg per day. No acute or chronic toxic effects were observed (*57*). The acute median lethal dose (LD_{50}) of anethole in rats was 3.8 mg/kg bw after intragastric administration (*58, 59*). Intragastric or subcutaneous administration of 10.0–16.0 g/kg bw of a 50% ethanol extract of the fruits to mice had no toxic effects (*60*). The oral LD_{50} of an essential oil from the fruits in mice was 1326.0 mg/kg bw (*61*).

Chronic use of high doses of *trans*-anethole in rodent dietary studies has been shown to induce cytotoxicity, cell necrosis and cell proliferation. In rats, hepatotoxicity was observed when dietary intake exceeded 30.0 mg/kg bw per day (*62*). In female rats, chronic hepatotoxicity and a low incidence of liver tumours were reported with a dietary intake of trans-anethole of 550.0 mg/kg bw per day, a dose about 100 times higher than the normal human intake (*62*). In chronic feeding studies, administration of *trans*-anethole, 0.25%, 0.5% or 1% in the diet, for 117–121 weeks had no effect on mortality or haematology, but produced a slight increase in hepatic lesions in the treated groups compared with controls (*63*).

Unscheduled DNA synthesis was not induced in vitro by anethole, but was induced by estragole, an effect that was positively correlated with rodent hepatocarcinogenicity (*64*). However, the dose of estragole used (dose not specified) in the rodent studies was much higher than the dose normally administered to humans. Low doses of estragole are primarily metabolized by O-demethylation, whereas higher doses are metabolized primarily by 1'-hydroxylation, and the synthesis of 1'-hydroxyestragole, a carcinogenic metabolite of estragole (*65, 66*).

Clinical pharmacology

No information available.

Adverse reactions

In rare cases, allergic reactions such as asthma, contact dermatitis and rhinoconjunctivitis have been reported in sensitive patients (*67, 68*).

Contraindications

The fruits are contraindicated in cases of known sensitivity to plants in the Apiacaeae (*69, 70*). Owing to the potential estrogenic effects of the essential oil from the seeds and anethole (*44, 45, 50*), its traditional use as an emmenagogue, and the lack of human studies demonstrating efficacy, Fructus Foeniculi should not be used in pregnancy. Pure essential oils should not be given to infants and young children owing to the danger of laryngeal spasm, dyspnoea and central nervous system excitation (*12*).

Warnings

The pure essential oil from the fruits may cause inflammation, and has an irritant action on the gastrointestinal tract.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the fruits, up to 100.0 mg/ml, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation with homogenized rat liver microsomes (*71, 72*). Aqueous and methanol extracts of the fruits, up to 100.0 mg/ml, were not mutagenic in the *Bacillus subtilis* recombination assay (*71*). However, a 95% ethanol extract, 10.0 mg/plate, was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102 (*73*). An essential oil from the fruits, 2.5 mg/plate, had mutagenic effects in the *Salmonella*/microsome assay in *Salmonella typhimurium* strain TA100 with metabolic activation (*74*), and in the *Bacillus subtilis* recombination assay (*75*). A similar essential oil had no effects in the chromosomal aberration test using Chinese hamster fibroblast cell lines (*76*).

Pregnancy: teratogenic effects

An essential oil from the fruits, up to 500.0 µg/ml, had no teratogenic effects in cultured rat limb bud cells (*61*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds.

Paediatric use
No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds. See also Contraindications.

Other precautions
No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test reactions.

Dosage forms
Dried fruits, syrup and tinctures. Store the dried fruits in a well-closed container, protected from light and moisture (*7*).

Posology
(Unless otherwise indicated)
Daily dose: fruits 5–7 g as an infusion or similar preparations, higher daily doses (> 7 g fruits) should not be taken for more than several weeks without medical advice (*25*); fennel syrup or honey 10–20 g; compound fennel tincture 5–7.5 g (5–7.5 ml).

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Radix Gentianae Luteae

Definition

Radix Gentianae Luteae consists of the dried roots and rhizomes of *Gentiana lutea* L. (Gentianaceae) (*1–6*).

Synonyms

Asterias lutea Borckh., *Swertia lutea* Vest (*2, 7*).

Selected vernacular names

Bachaka, bachalchaka, balmoney, common gentian, daoua el hoya, esperou, European gentian, felwort, gall weed, gansona, ganssana, Gelber Enzian, genchiana, genciana, genciana amarilla, gentian, gentiana, genziana gialla, genziana maggiore, gentiane, gentiane jaune, grande gentiane, great yellow gentian, jintiana, juntiyana, kaf edheeb, kaf el arnab, kouchâd, kouched, pale gentian, tárnics, wild gentian (*2, 6–10*).

Geographical distribution

Indigenous to mountainous regions of central and southern Europe (*6, 8, 11, 12*).

Description

A perennial herb up to 1.5 m high, with erect rhizomes. Stem thick, hollow, bearing large, opposite, ovate leaves with five to seven nerves and axillary cymes of orange-yellow, open-stellate flowers. Roots beet-like, thickened and branched, starting from a short rhizome. Fruits ovate, capsules containing winged seeds (*2, 8*).

Plant material of interest: dried roots and rhizomes

General appearance

Nearly cylindrical pieces, 3–20 cm long, 2–4 cm in diameter. Rhizome short, with fine, transverse wrinkles, and sometimes with buds and remains of leaves at the upper edge. Root longitudinally and deeply wrin-

kled, and more or less twisted; fractured surface yellow-brown and not fibrous; cambium and its surroundings tinged dark brown (*1, 2, 5*).

Organoleptic properties
Odour: characteristic; taste: initially sweet, becoming persistently bitter (*1, 2, 4, 5*). Bitterness value not less than 10 000 (*4*).

Microscopic characteristics
Transverse section of the root shows a narrow zone of four to six layers of thin-walled cork cells; a cork cambium, a broad zone of secondary cortex with brown, thin-walled parenchyma cells, practically devoid of starch, but containing oil globules and minute acicular crystals; a narrow zone of phloem composed of many layers of collapsed phloem parenchyma and numerous strands of sieve tubes; a distinct cambium; and a broad xylem composed largely of yellowish-brown to yellow, thin-walled wood parenchyma, scattered through which are a few large vessels and some tracheids, isolated or in small groups. Medullary rays indistinct. Transverse section of the rhizome exhibits a similar structure except for islets of sieve tissue in the xylem, a central pith and a collenchymatous phelloderm. Longitudinal sections of rhizome and root exhibit reticulate and scalariform tracheae and tracheids with non-lignified walls (*8*).

Powdered plant material
Moderate yellowish-brown to yellowish-orange. Fragments of reticulate, scalariform and pitted vessels and tracheids; fragments of brownish cork tissue, frequently adhering to which are thick-walled cells, numerous somewhat collapsed, large parenchyma cells; occasional clumps of minute slender prismatic crystals of calcium oxalate (3–6 µm long) in angles of parenchyma cells; starch grains few or absent. Stone cells and fibres absent (*3, 8*).

General identity tests
Macroscopic and microscopic examinations (*1, 2, 4–6*) and microchemical tests (*1, 2, 5*), and thin-layer chromatography (*4, 5*) for detection of adulteration with other *Gentiana* species (*4*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter
Not more than 2% (*1, 2*).

Total ash
Not more than 6% (*2, 4, 5*).

Acid-insoluble ash
Not more than 3% (*1, 5*).

Water-soluble extractive
Not less than 33% (*4*).

Loss on drying
Not more than 10% (*1, 2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*4*). For other pesticides, see the *European pharmacopoeia* (*4*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

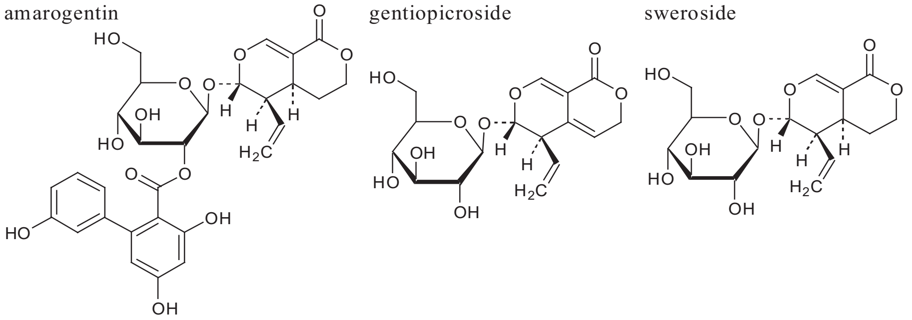
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash and alcohol-extractive tests to be established in accordance with national requirements.

Chemical assays
High-performance liquid chromatography for the presence of gentiopicroside and amarogentin (*15–17*).

Major chemical constituents
The major constituents are bitter secoiridoid monoterpenes including gentiopicroside (gentiopicrin; 2–8%, sometimes up to almost 10%), swertiamarin, sweroside (0.05–0.08%) and its acylglucoside derivative, amarogentin (0.03–0.08%), which is the bitterest of all compounds in this mat-

erial. Other constituents include xanthones (up to 0.1%), such as gentisin and isogentisin, gentianose (2.5–8.0%) and gentioside, the alkaloid gentianine, and traces of essential oil (*7, 10–12, 18, 19*). Representative structures of the secoiridoid monoterpenes are presented below:



Medicinal uses

Uses supported by clinical data

None. For the results of three uncontrolled human studies, see Clinical pharmacology (*20–22*). Although the findings suggest that Radix Gentianae Luteae may be of benefit for the treatment of dyspepsia, data from controlled clinical trials are currently lacking.

Uses described in pharmacopoeias and well established documents

Treatment of digestive complaints, such as loss of appetite, feeling of distension and flatulence (*23*). As an appetite stimulant during convalescence (*24*).

Uses described in traditional medicine

As a carminative, depurative, emmenagogue, febrifuge, tranquillizer and tonic, and to facilitate labour (*8, 10*). Treatment of diabetes and dysmenorrhoea (*10*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A 95% ethanol extract of Radix Gentianae Luteae (concentration not specified) inhibited the growth of *Staphylococcus aureus*, but was not active against *Escherichia coli* (*25*). A chloroform extract of the roots and rhizomes, 1.0 g/l, was not active against *S. aureus* (*26*). An aqueous extract of the roots and rhizomes, 500.0 mg/ml, inhibited the growth of the fungi *Aspergillus fumigatus, A. niger, Botrytis cinerea, Fusarium oxysporum* and *Penicillium digitatum* in vitro (*27*).

Antispasmodic activity

A 30% ethanol extract of the roots and rhizomes, 300 mg/l, inhibited acetylcholine- and histamine-induced contractions in guinea-pig ileum in vitro (*28*). The essential oil of Radix Gentianae Luteae induced relaxation of smooth muscles in isolated guinea-pig trachea and ileum with median effective doses of 108.0 mg/l and 76.0 mg/l, respectively (*29*).

Choleretic activity

Intragastric administration of a 95% ethanol extract of the roots and rhizomes (dose not specified) to rats was reported to exert a choleretic effect, while an aqueous or methanol extract was not active (*30*, *31*). Intraduodenal administration of 500 mg/kg body weight (bw) of a 95% ethanol extract of roots and rhizomes had choleretic effects in rats (*32*).

Secretory activity

Perfusion of a 30% ethanol extract of the roots and rhizomes, 4%, into the stomach of anaesthetized rats increased gastric secretions by 37.0% (*28*). Oral administration of a single dose of 5.0 g of an infusion of the roots and rhizomes to ewes stimulated the secretion of digestive enzymes in the small intestine (*33*).

Intragastric administration of the equivalent of 12.6 mg/kg bw of an alcohol extract of the roots and rhizomes per day for 3 days increased bronchial secretions in treated rabbits as compared with control animals (*34*).

Toxicology

The acute median lethal dose of a 30% ethanol extract of the roots and rhizomes in mice was 25.0 ml/kg (*28*). Intragastric administration of 1.6 ml/kg bw of a combination product containing alcohol extracts of Radix Gentianae, chamomile and liquorice per day for 13 weeks to rats produced no adverse effects and no changes in haemoglobin, red blood cells, packed cell volume, mean corpuscle haemoglobin concentration, total and differential white blood cell count or blood glucose. Histological examination showed no pathological changes in any organ system (*35*). Intragastric administration of 12.6 mg of an alcohol extract of the roots and rhizomes per day (treatment period not specified) to rabbits did not induce any symptoms of toxicity, with the exception of slightly lower erythrocyte concentrations in the treatment group compared with controls (*34*).

Clinical pharmacology

In one study without controls, oral administration of a single dose of 0.2 g of an ethanol extract of the roots 5 minutes prior to a meal

stimulated the secretion of gastric juice (*20*). In the same study, oral administration of 0.2 g of the extract stimulated and prolonged gall bladder secretions as observed by X-ray contrast (*20*). In another uncontrolled clinical trial, 19 patients with colitis ulcerosa, Crohn disease, or other non-specific inflammatory disorders and elevated secretory immune globulin (IgA) concentrations were treated with 20 drops of a tincture of the roots and rhizomes three times per day for 8 days. A control group of healthy volunteers received the same treatment. The IgA levels in both groups dropped and no statistical difference between the two groups was observed (*21*).

A multicentre trial, without controls, assessed the effect of the roots and rhizomes on the symptoms of dyspepsia in 205 patients. Each patient received five capsules containing 120.0 mg of a 5:1 dry ethanol extract of the roots and rhizomes per day. Patients reported relief of symptoms such as constipation, flatulence, appetite loss, vomiting, heartburn, abdominal pain and nausea (*22*).

Adverse reactions

On rare occasions, headaches may occur (*23*).

Contraindications

Owing to potential mutagenic activity (*36–38*), and its traditional use as an emmenagogue (*10*), Radix Gentianae Luteae should not be administered during pregnancy or nursing, or to small children. Radix Gentianae Luteae is contraindicated in gastric or duodenal ulcer, high blood pressure (*11*) and hyperacidity (*7, 24*).

Warnings

No information available.

Precautions

General

If symptoms persist, consult a physician. Overdose may lead to nausea or vomiting (*7, 24*).

Carcinogenesis, mutagenesis, impairment of fertility

Intragastric administration of 1.6 ml/kg bw of a combination product containing a 40% ethanol extract of Radix Gentianae Luteae, chamomile and liquorice per day for 13 weeks produced no effects on reproduction, fertility or mating in female rats and rabbits (*35*).

The mutagenicity of a methanol extract of Radix Gentianae Luteae, and two isolated minor hydroxyxanthone constituents, gentisin and isogentisin, was assessed in vitro. The methanol extract was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strain TA100 with metabolic activation with rat liver homogenate S9 enzyme mix. Gentisin and isogentisin, up to 50 µg/plate, were mutagenic after similar metabolic activation in *S. typhimurium* strains TA97, TA98, TA100 and TA2637 (*36–38*).

Pregnancy: teratogenic effects
Intragastric administration of 1.6 ml/kg bw of a combination product containing alcohol extracts of Radix Gentianae, chamomile and liquorice per day for 13 weeks had no teratogenic effects in rabbits (*35*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms

Dried roots and rhizomes; dried extracts of the roots and rhizomes for infusions, elixir, extracts, fluidextracts, glycerinated elixir and tinctures (*8, 23*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average adult daily dose: 0.1–2 g of the roots and rhizomes in 150 ml of water as an infusion, decoction or maceration, up to three times per day; fluidextract, 2–4 g; tincture (1 part roots and rhizomes:5 parts ethanol 45–70 % v/v) 1 ml three times per day; hydroethanolic extracts with an equivalent bitterness value (*7, 8, 11, 24*).

To stimulate the appetite, administer a single dose of a Radix Gentianae Luteae preparation one hour prior to meals (*11*); for dyspepsia, a single dose after a meal (*7, 24*).

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Radix Gentianae Scabrae

Definition

Radix Gentianae Scabrae consists of the dried roots and rhizomes of *Gentiana scabra* Bunge (Gentianaceae) (*1–4*).

Synonyms

Gentiana buergeri Miq., *G. fortunei* Hook. (*5*).

Selected vernacular names

Chinese gentian, dancao, Japanese gentian, kudancao, longdan, longdancao, tourindou (*1, 2, 4, 6, 7*).

Geographical distribution

Indigenous to the Korean peninsula and to China and Japan (*8, 9*).

Description

A perennial herb. Roots white, 10–15 cm long, with numerous short branches. Rhizomes rather short. Stems 20–100 cm long, with 10–20 pairs of leaves. Leaves lanceolate to narrowly deltoid-ovate, 4–8 cm long, 1–3 cm wide, gradually acuminate, three-nerved, green above, paler beneath, usually sessile, margin of upper leaves papillose. Flowers few to rather numerous, sessile, 4.5–6 cm long, purplish-blue; calyx tube 12–18 mm long, the lobes rather unequal, linear-lanceolate; corolla plaits deltoid, often toothed. Capsules stipitate, not exerted; seeds broadly lanceolate, short-caudate at both ends (*10, 11*).

Plant material of interest: dried roots and rhizomes

General appearance

Irregular, cylindrical, short yellowish-brown to greyish-brown rhizome with numerous slender roots. Roots 10–15 cm long, about 0.3 cm in diameter, with longitudinal, coarse wrinkles on the outer surface; flexible, fractured surface, smooth, yellow-brown. Rhizome about 2 cm long, 0.7 cm in diameter, with buds or short remains of stems at the top (*2*).

Organoleptic properties
Odour: characteristic; taste: bitter (*1–4*).

Microscopic characteristics
Root section shows epidermis, endodermis and a few layers of primary cortex; usually the outermost layers of the endodermis consisting of characteristic cells divided into a few daughter cells, often with collenchyma of one to two layers in contact with the inner side; secondary cortex having rents here and there, and irregularly scattered sieve tubes; vessels ranging rather radially in the xylem, and sieve tubes existing in the phloem. Root and rhizomes have distinct pith, rarely with sieve tubes, and parenchymatous cells containing needle, plate or rhombic crystals of calcium oxalate, and oil droplets. Starch grains mostly absent (*1, 2, 4*).

Powdered plant material
Fragments of parenchymatous cells containing oil droplets and minute needle crystals of calcium oxalate. Cells of exodermis spindle-shaped in surface view, each cell divided by transverse walls into several small rectangular cells. Cells of endodermis subrectangular in surface view, fairly large, periclinal walls showing minute transverse striations, each cell divided by longitudinal septa walls into several small palisade-like cells, longitudinal septa mostly beaded. Vessels mainly reticulate and scalariform, 20–30 µm but can be up to 45 µm in diameter (*2, 4*).

General identity tests
Macroscopic and microscopic examinations (*1–4*), microchemical tests (*1, 3*) and thin-layer chromatography (*2, 4*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*12*).

Total ash
Not more than 7% (*1–4*).

Acid-insoluble ash
Not more than 3% (*1–3*).

Alcohol-soluble extractive
Not less than 30% (*3*).

Loss on drying
Not more than 8% (*3*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*13*). For other pesticides, see the *European pharmacopoeia* (*13*), and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*14*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*12*).

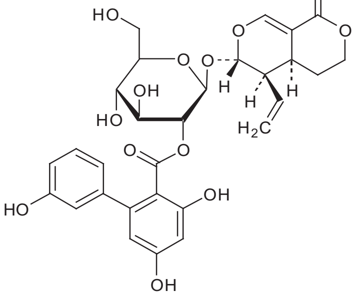
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter and water-soluble extractive tests to be established in accordance with national requirements.

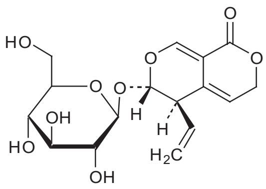
Chemical assays
Contains not less than 1.0% gentiopicroside determined by high-performance liquid chromatography (*4*).

Major chemical constituents
The major constituents are bitter secoiridoid monoterpenes including gentiopicroside (gentiopicrin; 0.5–10%), swertiamarin and sweroside. Xanthones, the alkaloid gentianine (0.05%) and gentianadine are other significant constituents. The bitter principle amarogentin found in *Gentiana lutea* is absent (*5, 7, 15–17*). Representative structures of the secoiridoid monoterpenes are presented below.

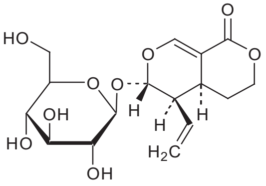
amarogentin



gentiopicroside



sweroside



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of liver disorders, cholecystitis and lack of appetite (*3, 6*).

Uses described in traditional medicine

Treatment of convulsions, eczema, fungal infections, hearing impairment, inflammation, leukorrhoea, otitis media, urinary tract infections, herpes zoster and pruritus vulvae (*3, 6, 7*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A 90% ethanol extract of the roots did not inhibit the growth of *Bacillus subtilis*, *Candida albicans, Escherichia coli, Staphylococcus aureus* or *Streptococcus faecalis* in vitro (*18*). An infusion of Radix Gentianae Scabrae had no antiviral activity in vitro when tested against herpes simplex virus 1, measles virus or poliovirus 1 (*19*).

Antihepatotoxic activity

Intraperitoneal administration of 1.0 g/kg body weight (bw) of a dried methanol extract of the roots and rhizomes, dissolved in normal saline, inhibited hepatotoxicity induced by carbon tetrachloride in rats but did not decrease the activity of alkaline phosphatase (*20*). Intraperitoneal administration of 1.0 g/kg bw of a dried methanol extract of the roots and rhizomes, dissolved in normal saline, to rats decreased increased glutamate-oxaloacetate transaminase activity induced by treatment with α-naphthylisothiocyanate and decreased plasma bilirubin concentrations, but did not decrease the activities of glutamate-pyruvate transaminase or lactate dehydrogenase (*20*). Intragastric administration of 670.0 mg/kg bw of a 1-butanol, chloroform or methanol extract of the roots and rhizomes prevented hepatotoxicity induced by carbon tetrachloride in mice (*21, 22*). The 1-butanol and chloroform extracts also inhibited the increased glutamate-pyruvate transaminase activity induced by carbon tetrachloride (*20*). Intraperitoneal administration of an aqueous or dried 50% methanol extract of the roots and rhizomes (dose not specified) prevented hepatotoxicity induced by carbon tetrachloride in mice (*23*). Intraperitoneal administration of 25.0–50.0 mg/kg bw of gentiopicroside

inhibited liver injury induced by D-galactosamine/lipopolysaccharide in mice (*24*). Intraperitoneal pretreatment of mice with 30.0–60.0 mg/kg bw of gentiopicroside per day for 5 days, suppressed the increased concentrations of serum hepatic aminotransferases induced by carbon tetrachloride (*25*).

Anti-inflammatory activity
Intraperitoneal administration of 90.0 mg/kg bw of gentianine to rats reduced swelling and inflammation of the ankle joint of the hind leg induced by formalin or egg white (*26, 27*).

Antispasmodic activity
A 95% ethanol extract of the roots and rhizomes, 200.0 µg/ml, did not inhibit barium- or histamine-induced smooth muscle contractions in guinea-pig ileum in vitro; however, an aqueous extract, 200.0 µg/ml, inhibited barium-induced contractions (*28*). The essential oil of Radix Gentianae Scabrae induced relaxation of smooth muscles in guinea-pig trachea and ileum in vitro, with median effective doses of 108.0 mg/l and 76.0 mg/l, respectively (*29*).

Central nervous system effects
Intraperitoneal administration of 250.0 mg/kg bw of a methanol or 75% methanol extract of the roots and rhizomes per day for 3 days to mice did not enhance the effects of barbiturates or increase hexobarbital-induced sleeping times (*30–32*). Intragastric administration of 670.0 mg/kg bw of a 1-butanol or chloroform extract of the roots did not potentiate the effects of barbiturates in mice (*20*). An ethanol extract of the roots and rhizomes (concentration not specified) inhibited the reuptake of serotonin in rat brainstem neurons in vitro (*33*). Intraperitoneal administration of 25.0–100.0 mg/kg bw of gentianine or gentianadine potentiated the anaesthetic effects of pentobarbital and chloral hydrate in mice (*6*). Intragastric administration of 200.0–400.0 mg/kg bw of gentianine or 700.0–1000.0 mg/kg bw of gentianidine resulted in sedation and reduced spontaneous activity in mice (*6*).

Choleretic activity
Intraduodenal administration of 50.0 g/kg bw of an aqueous extract of the roots and rhizomes to healthy rats or rats with hepatic injuries increased bile flow. A similar effect was observed in healthy dogs after intravenous administration of 4.5 g/kg bw of the extract (*6*). Intragastric administration of 1.8 g/kg bw of a dried methanol extract of the roots and rhizomes had choleretic effects in rats (*34*).

Toxicology
The oral median lethal doses (LD_{50}) of gentianine and gentianadine in mice were 400.0 mg/kg bw and 1250.0 mg/kg bw, respectively (*6, 35*). The subcutaneous LD_{50} of gentianine in mice was > 500.0 mg/kg bw, and the intravenous LD_{50} was 250.0–300.0 mg/kg bw (*6*). The intraperitoneal LD_{50} of a 90% ethanol extract of the roots and rhizomes in mice was 1.0 g/kg bw (*18*). 2-Hydroxy-3-methoxybenzoic acid glucose ester isolated from the roots and rhizomes was found to be a potent antagonist of platelet-activating factor in vitro (*36*).

Clinical pharmacology
No information available.

Adverse reactions
Radix Gentiana Scabrae may cause impairment of digestion and, occasionally, headaches, flushing of the face and vertigo when taken after a meal (*37*).

Contraindications
Owing to potential mutagenic effects (*38*), Radix Gentianae Scabrae should not be used during pregnancy or nursing or in children under the age of 12 years. Radix Gentianae Scabrae is contraindicated in stomach disorders and liver failure (*3*).

Warnings
Overdose may lead to nausea or vomiting (*3*).

Precautions
Carcinogenesis, mutagenesis, impairment of fertility
An aqueous extract of the roots and rhizomes, 40.0 mg/plate or 50.0 mg/disc, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 (*39, 40*). In another investigation, an aqueous or methanol extract of the roots and rhizomes, 100.0 mg/ml, was active in the *Salmonella*/microsome assay and the *Bacillus subtilis* recombination assay (*38*). However, intraperitoneal injection of an aqueous extract of the roots and rhizomes at doses 10–40 times those used in traditional medicine had no mutagenic effects in mice (*40*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; or teratogenic effects during pregnancy.

Dosage forms
Dried roots and rhizomes and dried extracts for infusions and decoction (*3, 4*). Store in a tightly sealed container away from heat and light.

Posology
(Unless otherwise indicated)
Average daily dose: roots and rhizomes 3–6 g per day as an infusion or decoction (*4*).

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Gummi Gugguli

Definition

Gummi Gugguli consists of the air-dried oleo-gum resin exudate from the stems and branches of *Commiphora mukul* (Hook. ex Stocks) Engl. (Burseraceae) (*1–4*).

Synonyms

Balsamodendron mukul Hook. ex Stocks, *B. roxburghii* Stocks non Arn., *Commiphora roxburghii* (Stocks) Engl., *C. wightii* (Arn.) Bhandari (*2, 5*).

Selected vernacular names

Aflatan, baijahundana, bdellium, boe-jahudan, devadhüpa, gogil, gugaru, guggal, guggul, guggula, guggulu, gukkal, gukkulu, hill mango, Indian bdellium, Indian myrrh tree, itinnil, kiluvai, kondamamidi, koushikaka, kungiliyam, maisatchi, moghl, moghl-arabi, moghl-azragh, moghl-makki, moql, moqle-azraqi, mugul, mukul myrrh tree, pura, ranghan (*5–12*).

Geographical distribution

Indigenous to Bangladesh, India and Pakistan (*6, 7, 11, 13*).

Description

Woody, bushy shrub 1–4 m high. Stems and branches thorny, covered with wax and ash-coloured bark that peels into thin rolls. Leaves small, alternate, simple or trifoliate. Flowers unisexual or bisexual with a fuzzy calyx and a brownish-red corolla. Fruits are ovoid drupes that turn red when ripe (*6, 7, 13–15*).

Plant material of interest: dried oleo-gum resin

General appearance

Vermicular or stalactitic pale yellow or brown pieces; slightly sticky to touch; viscid and golden when fresh. Makes a milky emulsion in hot water; burns readily (*2, 3, 6, 16–18*).

Organoleptic properties
Odour: characteristic aromatic, balsamic; taste: aromatic, bitter, acrid (*2, 3, 6, 16*).

Microscopic characteristics
Not applicable.

Powdered plant material
Not applicable.

General identity tests
Macroscopic appearance (*2, 3, 6, 16–18*), ultraviolet spectrophotometry of an ethanolic solution (*2*), and thin-layer chromatography (*2, 19*), and high-performance liquid chromatography for the presence of guggulsterones (*2, 20*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*21*).

Foreign organic matter
Not more than 4% (*3, 4*).

Total ash
Not more than 5% (*3, 4*).

Acid-insoluble ash
Not more than 1% (*3, 4*).

Sulfated ash
Not more than 10% (*2*).

Water-soluble extractive
Not less than 53% (*3, 4*).

Alcohol-soluble extractive
Not less than 35% (*2*).

Ethyl acetate-soluble extractive
Not less than 25% (*2*).

Moisture
Not more than 14% (*18*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*22*). For other pesticides, see the *European pharmacopoeia* (*22*), and the WHO guidelines on quality control methods for medicinal plants (*21*) and pesticide residues (*23*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*21*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*21*) for the analysis of radioactive isotopes.

Other purity tests
Chemical tests to be established in accordance with national requirements.

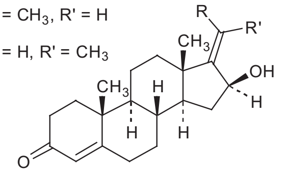
Chemical assays
Contains not less than 4.0% and not more than 6.0% of guggulsterones *Z* and *E* determined by high-performance liquid chromatography (*2*).

Major chemical constituents
A mixture of resins, essential oil (1.4–1.45%) (*13, 16*) and a water-soluble gum (made up of galactose, arabinose and 4-*O*-methylglucuronic acid (*5, 15*). The major constituents of the essential oil fraction of the oleo-gum resin are the monoterpene myrcene and the diterpene camphorene. The resinous fraction contains the diterpenes cembrene A and mukulol; the lignans sesamin and guggullignan-I and -II; and the sterols guggulsterol-I, -II, -III, -IV and -V, and *E*- and *Z*-guggulsterone (up to 15%) (*24*). *E*- and *Z*-guggulsterone are characteristic constituents that distinguish *Commiphora mukul* from other *Commiphora* species (*5, 11, 15, 17, 20, 25*). The structures of *E*- and *Z*-guggulsterones, guggulsterols-I, -II and -III, cembrene and mukulol are presented below.

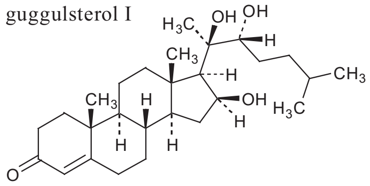
Medicinal uses
Uses supported by clinical data
Treatment of hyperlipidaemia and hypercholesterolaemia (*1, 26–33*). Clinical investigations to assess the use of extracts of the oleo-gum

(*E*)-guggulsterone R = CH_3, R' = H

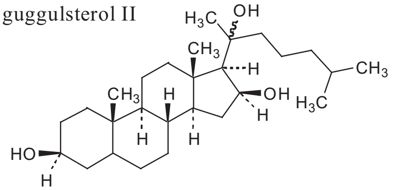
(*Z*)-guggulsterone R = H, R' = CH_3



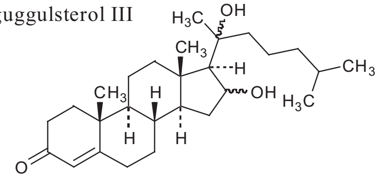
guggulsterol I



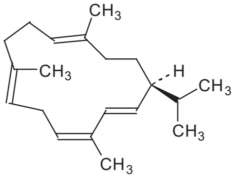
guggulsterol II



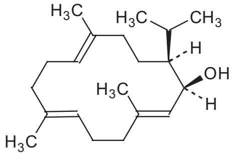
guggulsterol III



cembrene



mukulol



resin for the treatment of obesity were negative (*34, 35*) (see Clinical pharmacology).

Uses described in pharmacopoeias and well established documents

Treatment of atherosclerosis, rheumatic conditions, cough, sore throat and menopausal symptoms. As an emmenagogue (*3, 4, 8, 9, 16*).

Uses described in traditional medicine

Internally as an expectorant and for treatment of diarrhoea, fatigue, headache, jaundice and indigestion; topically for treatment of burns (*12, 16, 36–38*). Also as an insecticide and insect repellent (*9*).

Pharmacology

Experimental pharmacology

Anticoagulant activity

Intraperitoneal administration of 100.0 mg/kg body weight (bw) of an ethyl acetate extract of Gummi Gugguli to mice inhibited platelet aggregation (*39*). However, intraperitoneal administration of an aqueous extract of the oleo-gum resin to mice at the same dose was not active (*39*).

Antihypercholesterolaemic activity

Gummi Gugguli showed antihyperlipidaemic and antihypercholesterolaemic activities in animal models (*24, 40*). In chicks fed an atherosclerotic

diet, intragastric administration of a petroleum ether extract of the oleo-gum resin, 3.0 g/kg bw per day for 10 days or 2.0 g/kg bw per day for 30 days, significantly ($P < 0.001$) reduced serum cholesterol concentrations (*1*). In male chicks with estrogen-induced hyperlipidaemia, hypercholesterolaemia and weight gain, intragastric administration of 3 g/kg bw of a petroleum ether extract of the oleo-gum resin per day for 10 days reduced serum cholesterol concentrations and estradiol-induced weight gain (*1*). Histological examination showed an enhancement of the thyroid function in the treated animals, while suppression of thyroid function was observed in animals treated only with estradiol. In another study, intragastric administration of 5.0 mg/kg bw of a ketosteroid extract of the oleo-gum resin per day for one month to chicks fed an atherosclerotic diet and treated with carbimazole reduced serum cholesterol and triglyceride concentrations as compared with controls (*1*). In rats with dietary-induced hyperlipidaemia, administration of 10 mg/kg bw, 30 mg/kg bw or 100 mg/kg bw of an ethyl acetate fraction of the oleo-gum resin per day in the diet for 4 weeks significantly ($P < 0.001$) reduced total serum lipids and serum cholesterol, triglycerides and phospholipids (*9*). Similar hypolipidaemic effects of the oleo-gum resin have been observed in other animal species, such as dogs and monkeys (*41*).

The cholesterol-reducing activities of the oleo-gum resin are attributed to two closely related steroidal ketones, *trans*- and *cis*-guggulsterone (*E*- and *Z*-guggulsterone) (*20*). While the other chemical constituents do not have cholesterol-reducing activity individually, they act synergistically to enhance the overall antihypercholesterolaemic effects of the oleo-gum resin (*24*).

Anti-inflammatory activity

Intragastric administration of 500.0 mg/kg bw of an ethyl acetate fraction of the oleo-gum resin per day for a period of 5 months to rabbits decreased joint swelling induced by intra-articular injection of mycobacterial adjuvant (*42*). Intragastric administration of 400.0 mg/kg bw of an aqueous extract of the oleo-gum resin significantly ($P < 0.05$) reduced carrageenan-induced hind-paw oedema in rats by 59% (*43*). Administration of 400.0 mg/kg bw of a petroleum ether extract of the oleo-gum resin per day for 18 days to rats with arthritis induced by Freund's adjuvant significantly ($P < 0.05$) reduced the development of inflammation (*43*). Intraperitoneal administration of 200–400.0 mg/kg bw of a 100% ethanol extract of the oleo-gum resin reduced xylene-induced ear inflammation in mice by 50% (*44*). Intraperitoneal administration of 5.0 mg/kg bw of a steroid-containing fraction of a petroleum ether extract of the oleo-gum

resin to rats inhibited primary and secondary inflammation induced by Freund's adjuvant (*45*).

Antiobesity activity

Intragastric administration of 3.0 g/kg bw of the oleo-gum resin per day to rats and rabbits fed a high-fat and high-carbohydrate diet over a 4-month period reduced weight gain and the percentage of body fat (*1*). However, in rats fed a high-fat diet, treatment with 10.0 mg/kg bw, 30.0 mg/kg bw or 100.0 mg/kg bw of an ethyl acetate extract of the oleo-gum resin per day administered in the diet for 4 weeks did not reduce body weight as compared with controls (*9*).

Effects on thyroid function

Intragastric administration of a steroidal extract of 200.0 mg/kg bw of the oleo-gum resin per day for 15 days to mice induced triiodothyronine production and increased the triiodothyronine:thyroxine ratio (*46*). Intragastric administration of a ketosteroid isolated from a petroleum ether extract of 10.0 mg/kg bw of the oleo-gum resin per day for 6 days to rats significantly increased iodine uptake in the thyroid ($P < 0.05$) and enhanced the activities of thyroid peroxidase and protease ($P < 0.001$) (*40*).

Toxicology

Acute and chronic oral toxicity studies of an ethyl acetate extract of the oleo-gum resin were conducted in rats, mice and dogs (*47*). No mortality was observed in the 72 hours following administration of 5.0 mg/kg bw in all species. In dogs, no mortality was observed following oral administration of 1.0 g/kg bw per day over a period of 3 months. However, in rats, the mortality rate following administration of 250.0 mg/kg bw per day over the same period was 50%, compared with 20% in controls (*47*).

Clinical pharmacology

The effect of the oleo-gum resin was assessed in a parallel, placebo-controlled clinical trial in 40 patients with hyperlipidaemia: 20 patients received 4.5 g of the oleo-gum resin per day in two divided oral doses for 16 weeks; 20 controls received placebo administered at the same dose and in accordance with the same schedule. At the end of the 16-week treatment period, serum concentrations of cholesterol decreased by 21.75%; those of high-density lipids increased by 35.8% ($P < 0.01$) in the treated group as compared with controls. Serum triglyceride concentrations decreased by 27.1% in the treated group as compared with placebo control ($P < 0.01$) (*32*).

The hypolipidaemic effects of a standardized ethyl acetate extract of the oleo-gum resin containing approximately 4.0 g of *Z*- and *E*-gug-

gulsterones per 100.0 g of extract were compared with those of ethyl-*p*-chlorophenoxyisobutyrate (EPC) and a test substance (Ciba-13437-Su) in a randomized comparison trial in 44 patients with hyperlipidemia. Patients received 500.0 mg of oleo-gum resin extract twice per day, 500.0 mg of EPC three times per day, or 100.0 mg of the test substance three times per day for 6–36 weeks. Serum total lipids, cholesterol and triglycerides were measured before and after treatment. The oleo-gum resin extract significantly reduced total serum lipids by 34%, cholesterol by 27% and triglycerides by 29% ($P < 0.001$), and was as effective as or superior to the two other compounds tested (*26*).

A standardized ethyl acetate extract of the oleo-gum resin was compared with clofibrate in a long-term clinical trial. Of the 51 patients with hyperlipidaemia, 41 were treated with 1.5 g of the extract and 10 were treated with 2.0 g of clofibrate daily for a mean treatment period of 75 weeks. The extract significantly ($P < 0.001$) reduced serum cholesterol (26.2%) and triglycerides (36.5%). Clofibrate also significantly ($P < 0.001$) reduced total serum cholesterol (31.3%) and triglyceride concentrations (33.3%) (*28*).

In a phase I clinical trial to assess the safety of a standardized ethyl acetate extract of the oleo-gum resin, oral administration of 400.0 mg of the extract three times per day for 4 weeks to 21 hyperlipidaemic patients was safe and did not have any adverse effects on liver function, blood sugar, blood urea or haematological parameters (*30*). In a subsequent phase II clinical trial involving 19 patients with primary hyperlipidaemia (serum cholesterol > 250.0 mg/dl and serum triglycerides > 200.0 mg/dl), the same extract was administered orally, 500.0 mg three times per day for 12 weeks following 6 weeks of dietary control. Follow-up at 4-week intervals indicated that serum cholesterol and triglyceride concentrations were lowered in 15 patients (76.9%) after 4 weeks of treatment. The average decreases were 17.5% and 30.3%, respectively (*30*).

In a placebo-controlled trial, 120 obese patients with hyperlipidaemia received 2.0 g of the oleo-gum resin twice per day, 0.5 g of a petroleum ether fraction of the oleo-gum resin three times per day, a placebo daily or clofibrate daily for 21 days. The oleo-gum resin and clofibrate significantly decreased the mean serum cholesterol level after 10 days ($P < 0.01$ and $P < 0.1$, respectively). The petroleum ether fraction also significantly ($P < 0.05$) reduced serum cholesterol concentrations after 10 days of treatment as compared with placebo (*27, 29*).

Oral administration of 50.0 mg of an ethyl acetate extract of the oleo-gum resin or placebo capsules twice per day for 24 weeks as adjuncts to a fruit- and vegetable-enriched diet were compared for the management of

61 patients with hypercholesterolaemia in a randomized, double-blind study (*33*). The oleo-gum resin decreased the serum levels of total cholesterol (11.7%), low-density lipoprotein cholesterol (12.5%) and triglycerides (12.0%) in the treated group as compared with placebo; blood lipid peroxides, indicating oxidative stress also declined (33.3%) (*33*).

The effects of an ethyl acetate extract of the oleo-gum resin on serum cholesterol, fibrinolytic activity and platelet adhesive index were assessed in 20 healthy subjects and 20 subjects with cardiovascular disease. Both groups received 500.0 mg of the extract twice per day for 30 days. Serum fibrinolytic activity in the two groups increased by 22% and 19% in healthy volunteers and patients with cardiovascular disease, respectively, after 24 hours, and by 40% and 30% after 30 days; platelet adhesive index decreased by 19% and 16%. There was no decrease in serum cholesterol concentrations (*48*).

In a controlled clinical trial, 75 subjects were divided into three groups of 25 subjects, which received placebo, encapsulated oleo-gum resin (16.0 g) or a petroleum ether extract of the oleo-gum resin (dose equivalent to that of the oleo-gum resin) daily for 3 months. Serum cholesterol levels were significantly reduced in both treatment groups as compared with controls: by 24.2% ($P > 0.001$) in the oleo-gum resin group; and by 30.0% ($P > 0.001$) in the extract group (*1*).

In a double-blind, placebo-controlled clinical trial, 62 subjects, at least 10% overweight, received 1.5 g of an ethyl extract of the oleo-gum resin or matching placebo daily for 4 weeks. The extract significantly ($P < 0.01$) decreased (~10%) total serum cholesterol compared with placebo. However, there was no effect on body weight in either group (*34*).

In a randomized double-blind, placebo-controlled clinical trial, 84 obese subjects, at least 10% overweight, received 1.5 g of an ethyl acetate extract of the oleo-gum resin or matching placebo daily for 12 weeks. The extract significantly decreased (~20%) serum levels of total cholesterol ($P < 0.01$), total lipids ($P < 0.05$) and triglycerides ($P < 0.05$) compared with placebo. A slight, but significant reduction in body weight was observed at 4 weeks ($P < 0.05$) in the extract group, but at 12 weeks no significant effects on this parameter were observed (*35*).

Adverse reactions

In clinical trials, minor adverse effects such as mild diarrhoea and restlessness have been reported (*26, 28*). In one clinical trial of the oleo-gum resin, gastrointestinal upset was noted in 17.5% of patients (*27*). Topical application of a diluted (8%) aqueous solution of an essential oil obtained from the oleo-gum resin was non-irritating, non-sensitizing and non-

phototoxic (*1*). However, application of an extract (not further specified) to human skin caused contact dermatitis (*49–51*). In clinical trials, the oleo-gum resin and petroleum ether extracts of the oleo-gum resin were reported to shorten the menstrual cycle and increase menstrual flow (*1*).

Contraindications

Gummi Gugguli is used traditionally as an emmenagogue (*12*), and its safety during pregnancy has not been established. Therefore, in accordance with standard medical practice, the oleo-gum resin should not be used during pregnancy.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the oleo-gum resin, 40.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 (*52*). Intraperitoneal administration of an aqueous extract of the oleo-gum resin at a dose 10–40 times the normal therapeutic dose did not have mutagenic activity (*52*). A hot aqueous extract of the oleo-gum resin, 40.0 mg/plate, inhibited mutagenesis induced by aflatoxin B1 in *S. typhimurium* strains TA98 and TA100 (*53*).

Intragastric administration of the oleo-gum resin (dose not specified) reduced the weight of rat uterus, ovaries and cervix, with a concomitant increase in their glycogen and sialic acid concentrations, suggesting an antifertility effect (*54*).

Pregnancy: non-teratogenic effects

See Contraindications.

Other precautions

No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Powdered oleo-gum resin; petroleum ether or ethyl acetate extracts of the oleo-gum resin; other galenical preparations (*1, 26, 30, 32*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: oleo-gum resin 3–4.5 g in two or three divided doses (*30, 32*); petroleum ether extracts of the oleo-gum resin 500 mg two or three times (*26*).

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Radix Harpagophyti

Definition

Radix Harpagophyti consists of the dried, tuberous, secondary roots of *Harpagophytum procumbens* DC. ex Meiss. (Pedaliaceae) (*1, 2*).

Synonyms

Harpagophytum burcherllii Decne (*3*).

Selected vernacular names

Afrikanische Teufelskralle, beesdubbeltjie, devil's claw, duiwelsklou, grapple plant, grapple vine, harpagophytum, kanako, khams, khuripe, legatapitse, sengaparele, Teufelskralle, Trampelklette, wood spider xwate (*3–8*).

Geographical distribution

Indigenous to the Kalahari desert and savannas of Angola, Botswana, Namibia and South Africa, being found southwards from central Botswana (*6, 7, 9–11*).

Description

Prostrate perennial mat-forming herb, up to 1.5 m across. Tuber up to 6 cm in diameter, bark yellowish-brown, longitudinally striated. Leaves pinnately lobed and clothed with glandular hairs, the underside densely pubescent. Flowers bright red, solitary, rising abruptly from the leaf axils; corolla pentamerous, tubular, pink-purple, up to 7 cm long; androecium of four stamens with one staminodium. Fruits characteristically large, hooked, claw-like, tardily dehiscent two-locular capsules, flattened at right angles to the septum, the edges bearing two rows of woody arms up to 8 cm long with recurved spines (*6, 12, 13*).

Plant material of interest: dried, tuberous, secondary roots

General appearance

Irregular thick, fan-shaped or rounded slices or roughly crushed discs of tuber, 2–4 cm and sometimes up to 6 cm in diameter, 2–5 mm thick,

greyish-brown to dark brown. Darker outer surface traversed by tortuous longitudinal wrinkles. Paler cut surface shows a dark cambial zone and xylem bundles distinctly aligned in radial rows. Central cylinder shows fine concentric striations. Seen under a lens, the cut surface presents yellow to brownish-red granules, longitudinally wrinkled; transverse surface yellowish-brown to brown, central region raised, fracture short (*1, 2*).

Organoleptic properties

Odour: none; taste: bitter (*1, 2*).

Microscopic characteristics

Several rows of large, thin-walled cork cells frequently with yellowish-brown contents; parenchymatous cortex with very occasional sclereids with reddish-brown contents, xylem arranged in concentric rings; reticulately thickened vessels, some with rounded perforations in the end walls (tracheidal vessels); abundant lignified parenchymatous cells associated with the vessels and in the small central pith (*1*).

Powdered plant material

Brownish-yellow with fragments of cork layer consisting of yellowish-brown, thin-walled cells; fragments of cortical parenchyma consisting of large, thin-walled cells, sometimes containing reddish-brown granular inclusions and isolated yellow droplets; fragments of reticulately thickened vessels and tracheidal vessels with associated lignified parenchyma from the central cylinder; small needles and crystals of calcium oxalate present in the parenchyma. May show rectangular or polygonal pitted sclereids with dark reddish-brown contents. Parenchyma turns green when treated with a solution of phloroglucinol in hydrochloric acid (*2*).

General identity tests

Macroscopic and microscopic examinations, and thin-layer chromatography for the presence of harpagoside (*1, 2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Not more than 2% (*1, 2*).

Total ash
Not more than 8% (*2*).

Acid-insoluble ash
Not more than 5% (*1*).

Water-soluble extractive
Not less than 50% (*1*).

Loss on drying
Not more than 12% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

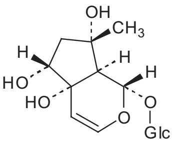
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 1.2% harpagoside as determined by high-performance liquid chromatography (*2*).

Major chemical constituents
The major active constituents are harpagoside and the related iridoid glycosides, harpagide and procumbide, which occur in lesser amounts. Total iridoid glycoside content 0.5–3.3% (*3, 7, 10, 11*). The structures of the major iridoid glycosides are presented below.

Medicinal uses
Uses supported by clinical data
Treatment of pain associated with rheumatic conditions (*17–24*).



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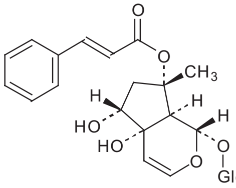

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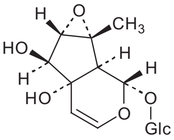
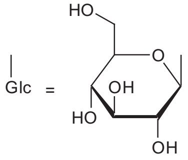


procumbide



β-D-glucopyranosyl

Uses described in pharmacopoeias and well established documents

Treatment of loss of appetite and dyspeptic complaints; supportive treatment of degenerative rheumatism, painful arthrosis and tendonitis (*25*).

Uses described in traditional medicine

Treatment of allergies, boils, diabetes, liver disorders and sores (*8*).

Pharmacology

Experimental pharmacology

Anti-inflammatory and analgesic activity

A 60% ethanol extract of Radix Harpagophyti, 100.0 µg/ml, standardized to contain 2.9% harpagoside, inhibited the release of tumour necrosis factor-α (TNF-α) induced by the treatment of human monocytes with lipopolysaccharide (LPS) in vitro. However, treatment of the monocytes with harpagoside and harpagide, 10.0 µg/ml, isolated from the roots, had no effect on LPS-induced TNF-α release (*26*). Harpagoside, 10.0–100.0 µmol/l, reduced the synthesis of thromboxane B_2 in cells treated with calcium ionophore A23187 (*27*).

The results of studies assessing the anti-inflammatory activity of Radix Harpagophyti in animal models are conflicting. Intragastric administration of 20.0 mg/kg body weight (bw) of an aqueous or methanol extract of the root to rats inhibited oedema and inflammation in the granuloma pouch and carrageenan-induced footpad oedema tests (*28*). Intragastric administration of 20 mg/kg bw of a methanol extract of the root inhibited erythema induced by ultraviolet light in rats (*28*). Intragastric administration of 20.0 mg/kg bw of the same methanol extract to mice exhibited analgesic activity in the hot-plate test, but did not inhibit benzoquinone-induced writhing (*28*). Intraperitoneal pretreatment of rats with an aqueous extract of the roots reduced carrageenan-induced footpad oedema in a dose-dependent manner. Doses of 400 mg/kg bw and 1200 mg/kg bw reduced oedema by 43% and 64%, respectively, 3 hours after administration. The efficacy of the higher dose was similar to that of indometacin, 10 mg/kg bw (*29*). Intraperitoneal administration of 400.0 mg/kg bw of a

chloroform extract of the roots to mice with carrageenan-induced footpad oedema and inflammation reduced inflammation by 60.3% 5 hours after treatment (*30*).

Intraperitoneal administration of 200–400 mg/kg bw of an aqueous extract of the roots reduced carrageenan-induced footpad oedema in rats, but did not increase the reaction time of mice in the tail-flick hot-plate test. The anti-inflammatory activity of the highest dose was more efficient in rats than indometacin, 10.0 mg/kg bw. Treatment of the aqueous extract with 0.1 mol/l hydrochloric acid dramatically decreased the activity, suggesting that oral dosage forms should be enteric coated to protect the active principles from stomach acid. In the same study, harpagoside did not appear to be involved in the anti-inflammatory activity (*31*).

Intraperitoneal administration of 20.0 mg/kg bw of an aqueous extract of the roots to rats reduced formalin-induced arthritis. The effectiveness was comparable to that of phenylbutazone, 50.0 mg/kg bw. This study also demonstrated that intraperitoneal administration of 10–50 mg/kg bw of harpagoside to rats inhibits both formalin- and albumin-induced footpad oedema and formalin-induced arthritis (*32*).

Intragastric administration of 200.0 mg of an aqueous extract of the roots to rats inhibited formalin-induced footpad oedema (*33*). However, another study showed that intragastric administration of 1.0 g/kg bw of the powdered roots to rats did not inhibit carrageenan-induced footpad oedema or adjuvant-induced arthritis, as compared with other anti-inflammatory agents such as indometacin or acetylsalicyclic acid (*34*). Investigations of the antiphlogistic activity of harpagoside, harpagide and an aqueous extract of Radix Harpagophyti (doses not specified) indicated that all three substances had anti-inflammatory activity similar to that of phenylbutazone (*35*). In mice, intragastric administration of 100.0 mg/kg bw of harpagoside inhibited carrageenan-induced footpad oedema, and external application of 1.0 mg/ear reduced ear oedema induced by phorbol ester (*36*).

Intragastric administration of up to 100 times the recommended daily dose of powdered roots (6.0 g/kg bw) to rats did not reduce footpad oedema induced by carrageenan or *Mycobacterium butyricum*. Furthermore, the root preparation, 100.0 mg/ml, failed to inhibit prostaglandin synthase activity in vitro (*37*).

Antiarrhythmic activity

Intragastric administration of 100 mg/kg bw of an aqueous or methanol extract of the roots protected rats against ventricular arrhythmias induced by epinephrine-chloroform or calcium chloride (*38*). Intraperitoneal administration of 25 mg/kg bw of a methanol extract of the roots inhibited

cardiac arrhythmias induced by aconitine, epinephrine-chloroform or calcium chloride in fasted rats (*38*). Intragastric administration of 300–400 mg/kg bw of a methanol extract of the roots to normotensive rats reduced heart rate and arterial blood pressure (*38*). Other studies have demonstrated that lower doses of the extract have slight negative chronotropic and positive inotropic effects (*39*), whereas larger doses have a marked inotropic effect, with reductions in coronary blood flow. The inotropic effect is attributed to harpagide (*40*).

Clinical pharmacology

Antidyspeptic activity

A decoction of Radix Harpagophyti is one of the strongest bitter tonics known (*41*). Ingestion of a tea prepared from the root (dose not specified) over a period of several days led to an improvement in the symptoms of disorders of the upper part of the small intestine, which were accompanied by disturbances of choleresis and bile kinesis (*41*). It has been proposed that, because the root is very bitter, is a good stomachic and stimulates the appetite, it may also be useful for the treatment of dyspeptic complaints (*17, 42, 43*).

Anti-inflammatory and analgesic activity

A randomized double-blind comparison study, involving 46 patients with active osteoarthritis of the hip, assessed the effects of oral administration of 480 ng of an ethanol extract of the roots twice daily in the successive reduction of ibuprofen use for pain and the Western Ontario and McMaster Universities (WOMAC) arthrosis index. Patients received, in conjunction with the extract or placebo, 800.0 mg of ibuprofen daily for 8 weeks, then 400.0 mg daily for 8 weeks, then no ibuprofen. After 20 weeks of treatment, the WOMAC index decreased in the treatment group, with improvements in pain, stiffness and loss of function (*23*). In a randomized, double-blind clinical trial in 122 patients suffering from osteoarthritis of the knee and hip, the efficacy and tolerance of the roots and diacerein were compared. Patients received the roots as 6 capsules per day, each containing 435.0 mg of powdered roots or 100.0 mg of diacerein daily for 4 months. Assessments of pain and functional disability were made on a 10-cm horizontal visual analogue scale, and the severity of osteoarthritis was evaluated using the Lequesne functional index. There was a reduction in spontaneous pain and a progressive reduction in the Lequesne index in both groups. Fewer side-effects were observed in the group treated with the powdered roots (8.1%) than in the group receiving diacerein (26.7%) (*22*).

In a double-blind, placebo-controlled clinical trial, 50 patients with various arthroses were treated with 1200.0 mg of a hydroalcoholic extract of the roots, containing 1.5% iridoid glycosides, daily for 3-week courses. The severity of pain was assessed 10 days after completion of treatment. Each patient was given one to three courses of treatment. Compared with placebo, the extract produced a decrease in the severity of pain in individuals with a moderate pain level (*44*).

In an uncontrolled study involving 630 patients with arthrosis, 42–85% of the patients showed improvements after 6 months of daily oral treatment with 3.0–9.0 g of an aqueous extract of the roots containing 2.5% of iridoid glycosides (*45*). In an uncontrolled trial, the efficacy of an orally administered aqueous extract of the roots (as tablets) was assessed in 13 patients, 11 with arthritis and two with psoriatic arthropathy. Treatment of the patients for 6 weeks with 1.23 g daily did not reduce pain or inflammation in 12 patients, and one patient withdrew owing to side-effects (*46*). In an uncontrolled study, beneficial results were reported in 80% of 60 patients with chronic polyarthritis after treatment with subcutaneous lateral and medial injections of aqueous root extracts on both sides of the knee joint (*17*).

The efficacy of a standardized hydroalcoholic extract of the roots for the treatment of chronic back pain was assessed in a double-blind, randomized, placebo-controlled trial. The 197 patients were treated orally with 600.0 mg or 1200.0 mg of the extract (standardized to contain a total of 50–100 mg of harpagoside) or placebo daily for 4 weeks. A total of 183 patients completed the trial. Three, six and ten patients in the placebo, low-dose extract and high-dose extract groups, respectively, ($P = 0.027$) remained pain-free without the permitted pain medication (tramadol) for 5 days in the last week (*20*). A 4-week randomized double-blind, placebo-controlled clinical trial assessed the safety and efficacy of an ethanol extract of the roots in the treatment of acute attacks of pain in 118 patients with chronic back problems. Patients received two 400.0-mg tablets three times per day (equivalent to 6 g of roots containing 50.0 mg of harpagoside). Intake of a supplementary analgesic (tramadol) did not differ significantly between the placebo and the treatment group. However, further analysis revealed that nine out of 51 patients who received the extract were pain free at the end of the treatment period, compared to only one out of 54 in the placebo group (*18*). The efficacy of a dried ethanol extract of the roots was investigated in a 4-week, double-blind, placebo-controlled study in 118 patients with a history of chronic lower back pain. Patients were randomly assigned to receive two tablets of the extract or placebo three times per day. After 4 weeks of treatment, a reduction in the

Arhus low back pain index was observed in the treated patients compared with those receiving placebo (*19*). A randomized, placebo-controlled, double-blind study investigated the effects of an ethanol extract of the roots on sensory, motor and vascular mechanism of muscle pain in 65 patients with mild to moderate muscle tension or mild back, shoulder or neck pain. Patients received two doses of 480.0 mg of the extract or placebo daily for 4 weeks. At the end of the treatment period, a significant reduction in muscle pain as measured by a visual analogue scale ($P < 0.001$) was observed in the extract group. Muscle stiffness and ischaemia were also improved in this group, but no changes were found in antinociceptive muscle reflexes or surface electromyography (*24*).

Oral administration of powdered roots, four 500.0-mg capsules, standardized to contain 3% total iridoids, daily for 21 days to healthy volunteers did not statistically alter eicosanoid biosynthesis by the cyclooxygenase or 5-lipoxygenase pathways. The results indicated that in healthy humans Radix Hapagophyti did not inhibit arachidonic acid metabolism (*47*).

Adverse reactions

Mild and infrequent gastrointestinal symptoms were reported in clinical trials (*18, 20, 45*).

Contraindications

Radix Harpagophyti is contraindicated in gastric and duodenal ulcers, and cases of known hypersensitivity to the roots (*25*). Owing to a lack of safety data, Radix Harpagophyti should not be used during pregnancy and nursing.

Warnings

No information available.

Precautions

General

Patients with gallstones should consult a physician prior to using the roots (*25*).

Drug interactions

An extract of the roots did not inhibit the activity of cytochrome P450 isoform 3A4 in vitro, suggesting that Radix Harpagophyti would not interact with prescription drugs metabolized by this enzyme (*48*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Other precautions
No information available on precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic effects during pregnancy; or paediatric use.

Dosage forms

Dried roots for decoctions and teas; powdered roots or extract in capsules, tablets, tinctures and ointments (*6, 7*). Store in a well closed container, protected from light (*2*).

Posology

(Unless otherwise indicated)
Daily dose: for loss of appetite 1.5 g of the roots in a decoction, 3 ml of tincture (1:10, 25% ethanol) (*25*); for painful arthrosis or tendonitis 1.5–3 g of the roots in a decoction, three times, 1–3 g of the roots or equivalent aqueous or hydroalcoholic extracts (*41*).

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Rhizoma Hydrastis

Definition
Rhizoma Hydrastis consists of the dried rhizomes and roots of *Hydrastis canadensis* L. (Ranunculaceae) (*1–3*).

Synonyms
Hydrastis canadensis was formerly classified as a member of the family Berberidaceae.

Selected vernacular names
Eyebalm, golden seal, goldenseal, gorzknik kanadyjski, ground raspberry, hydraste, hydrastis, idraste, Indian dye, Indian paint, Indian turmeric, sceau d'or, warnera, wild curcuma, yellow puccoon (*4, 5*).

Geographical distribution
Indigenous to North America (*4, 6*).

Description
A perennial herb. Underground portion consists of a horizontal, branching rhizome bearing numerous long slender roots. Aerial part consists of a single radical leaf and a short stem 10–18 cm high, which bears near its summit two petiolate, palmate (five to seven lobes), serrate leaves and ends with a solitary greenish-white flower. Fruits are compound crimson berries somewhat similar to raspberries (*4*).

Plant material of interest: dried rhizomes and roots

General appearance
Rhizomes horizontal or oblique, subcylindrical, 1–6 cm long, 2–10 mm in diameter, occasionally with stem bases; numerous short upright branches terminating in cup-shaped scars and bearing encircling cataphyllary leaves. Externally, brown-greyish or yellowish-brown, deep longitudinal wrinkles, marked by numerous stem and bud-scale scars. From the lower

and lateral surfaces, arise many long, slender, brittle, curved, and wiry roots, frequently broken off to leave short protuberances or circular, yellow scars. Fracture short and resinous; fractured surface yellowish-orange at centre and greenish-yellow at margin with thick, dark yellow to yellowish-brown bark. Bright yellow, narrow xylem bundles separated by wide medullary rays; large pith. Roots numerous, filiform up to 35 mm long and 1 mm in diameter, curved or twisted. Fracture short and brittle, fractured surface yellowish-orange to greenish-yellow (*1, 3, 4*).

Organoleptic properties

Odour: faint, unpleasant; taste: bitter, persistent (*1, 4, 6*).

Microscopic characteristics

Rhizome cork yellowish-brown, polygonal cells with thin lignified walls; secondary cortex contains abundant thin-walled, polygonal to round or elongated, parenchymatous cells and some collenchyma, with abundant starch grains, simple or rarely compound with two to six components, spherical or ovoid with small, round or slit-like hilum. Parenchyma contains numerous masses of granular, orange-brown matter. Lignified tracheids present, usually small with slit-like pits, but occasionally large vessels with reticulate thickening. Root cork consists of a single layer of cells, irregularly elongated. Very occasional fragments of piliferous layer from young roots with root hairs; and a few thin-walled, lignified fibres associated with vessels present. Occasional fragments of epidermis of stem bases composed of cells with thick, lignified, beaded walls, slightly elongated in surface view (*1, 3, 4*).

Powdered plant material

Dark yellow to moderate greenish-yellow. Numerous spherical, simple starch grains, 2–15 µm in diameter, the larger grains exhibiting a central hilum; a few compound forms with two to six components. Fragments of starch-bearing parenchyma and fibrovascular tissue. Tracheal elements with simple and bordered pores, some with spiral thickenings and wood fibres, 200–300 µm long, thin-walled and with simple pores. A few fragments of cork tissue, the cells of which have reddish-brown walls. Calcium oxalate crystals absent (*3, 4*).

General identity tests

Macroscopic and microscopic examinations (*1, 3, 4*), and thin-layer chromatography (*1, 3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

Chemical

Not less than 2.0% hydrastine and not less than 2.5% berberine (*3*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 9% (*3*).

Acid-insoluble ash

Not more than 5% (*3*).

Water-soluble extractive

Not less than 14% (*1*).

Loss on drying

Not more than 12% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*8*). For other pesticides, see the *European pharmacopoeia* (*8*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*9*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

Radioactive residues

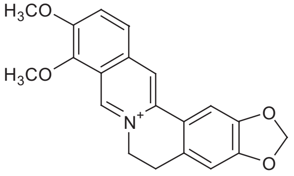
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*7*).

Other purity tests

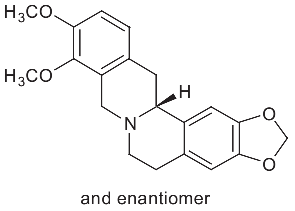
Sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 2.0% hydrastine and not less than 2.5% berberine determined by high-performance liquid chromatography (*3*).

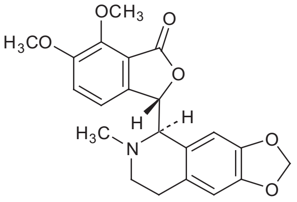
Major chemical constituents
The major constituents are isoquinoline alkaloids (2.5–6.0%), principally hydrastine (1.5–5.0%), followed by berberine (0.5–4.5%), canadine (tetrahydroberberine, 0.5–1.0%), and lesser quantities of related alkaloids including canadaline, corypalmine, hydrastidine and jatrorrhizine (*5, 10–13*). The structures of hydrastine, berberine and canadine (a mixture of α-canadine (*R*-isomer) and β-canadine (*S*-isomer)) are presented below:



berberine



canadine



hydrastine

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Treatment of digestive complaints, such as dyspepsia, gastritis, feeling of distension and flatulence (*1*).

Uses described in traditional medicine
Treatment of cystitis, dysmenorrhoea, eczema, haemorrhoids, uterine haemorrhage, inflammation, kidney diseases, menorrhagia, nasal congestion, tinnitus and vaginitis. As a cholagogue, diuretic, emmenagogue, haemostat, laxative and tonic (*5*).

Pharmacology
Experimental pharmacology
Antimicrobial activity
A methanol extract of Rhizoma Hydrastis and berberine inhibited the growth of *Helicobacter pylori* (the bacterium associated with dyspepsia, gastritis and peptic ulcer disease) in vitro, median inhibitory concentration

range 0.625–40.00 µg/ml (*14, 15*). A 95% ethanol extract of the rhizomes, 1.0 mg/ml, inhibited the growth of *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis* and *Candida albicans* in vitro (*16*). Berberine was the active constituent of the extract, minimum inhibitory concentration 25.0–50.0 µg/ml against *Staphylococcus aureus* and *Mycobacterium smegmatis* (*16, 17*). Berberine inhibited the growth of *Bacillus subtilis* and *Salmonella enteritidis* in vitro at concentrations of 1.0 mg/ml and 0.5 mg/ml, respectively (*18*). Berberine, 150.0 µg/ml, also inhibited the growth of *Clostridium perfringens* in vitro and, at 1.0 mg/ml, significantly ($P < 0.001$) inhibited the growth of and induced morphological changes in *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis* (*19*).

Effects on smooth muscle

A 70% ethanol extract of the rhizomes inhibited carbachol-induced contractions of isolated guinea-pig trachea in vitro, median inhibitory dose 1.6 µg/ml (*20*). In rabbit bladder detrusor muscle strips, an ethanol extract of the rhizomes inhibited contractions induced by isoprenaline, median effective concentration 40 nmol/l (*21*). An alcohol extract of the rhizomes reduced contractions induced by serotonin, histamine and epinephrine in isolated rabbit aortas (*22*). Investigations using the major alkaloids from the rhizomes assessed the antispasmodic mechanism of action in isolated guinea-pig tracheas (*23*). The median effective concentrations of berberine, β-hydrastine, canadine and canadaline were 34.2 µg/ml, 72.8 µg/ml, 11.9 µg/ml and 2.4 µg/ml, respectively. Timolol pretreatments antagonized the effects of canadine and canadaline, but not berberine or β-hydrastine (*23*).

Berberine, 1 µmol/l, induced relaxation of norepinephrine-precontracted isolated rat aortas (*24*). Berberine, 10^{-5} mol/l, induced relaxation in isolated precontracted rat mesenteric arteries (*25, 26*). Berberine, 0.1–100.0 µmol/l, suppressed basal tone and induced a concentration-dependent relaxation of phenylephrine-precontracted rabbit corpus cavernosum (*27*). Intracavernosal injection of 5.0 mg/kg of berberine to anaesthetized rabbits increased intracavernosal pressure from 12.7 mmHg to 63.4 mmHg, duration of tumescence ranging from 11.5 to 43.7 minutes (*27*). A hydroalcoholic extract of the rhizomes or berberine inhibited norepinephrine- and phenylephrine-induced contractions in isolated rabbit prostate strips with ED_{50} values of 3.92 µmol/l and 2.45 µmol/l, respectively (*28*).

Immunological effects

Intragastric administration of an extract (type not specified) of the rhizomes, 6.6 g/l in drinking-water, to rats for 6 weeks increased production of antigen-specific immunoglobulin M (*29*). Intraperitoneal administra-

tion of 10.0 mg/kg body weight (bw) of berberine per day for 3 days to mice before the induction of tubulointerstitial nephritis significantly ($P = 0.001$) reduced pathological injury, improved renal function, and decreased the numbers of CD3+, CD4+ and CD8+ T-lymphocytes (*30*).

Toxicology

The oral median lethal dose of berberine in mice was 329.0 mg/kg bw (*31*). Oral administration of 2.75 g of berberine to dogs produced severe gastrointestinal irritation, profuse watery diarrhoea, salivation, muscular tremors and paralysis; respiration was not affected. Postmortem examination showed the intestines to be contracted, inflamed and empty or containing mucous and watery fluid. Oral administration of berberine sulfate, 25.0 mg/kg bw, induced central nervous system depression in dogs lasting 6–8 hours; 50.0 mg/kg bw caused salivation and sporadic emesis; 100.0 mg/kg bw induced persistent emesis and death of all animals 8–10 days later (*31*).

Uterine stimulant effects

Hot aqueous extracts of the rhizomes, 1:200 in the bath medium, stimulated contractions in isolated guinea-pig uteri (*32*). However, an alkaloid-enriched extract of the rhizomes did not stimulate contractions in isolated mouse uteri (*33*). A 70% ethanol extract of the rhizomes inhibited spontaneous and oxytocin- and serotonin-induced contractions in isolated rat uteri, median inhibitory concentrations 10.0–19.9 μg/ml (*20*).

Clinical pharmacology

No controlled clinical studies available for Radix Hydrastis. While berberine has been shown to be effective for the treatment of bacterially-induced diarrhoea (*34–40*), ocular trachoma (*41*) and cutaneous leishmaniasis (*42–44*), the data cannot generally be extrapolated to include extracts of the rhizomes.

Adverse reactions

No information available on adverse reactions to Radix Hydrastis. However, high doses of hydrastine are reported to cause exaggerated reflexes, convulsions, paralysis and death from respiratory failure (*45*).

Contraindications

Radix Hydrastis is contraindicated in cases of known allergy to the plant material.

Warnings

No information available.

Precautions

General

Use with caution in patients with high blood pressure, diabetes, glaucoma and a history of cardiovascular disease.

Drug interactions

An ethanol extract of the rhizomes inhibited the activity of cytochrome P450 (CYP3A4) in vitro, median inhibitory concentration <1% (*46*). Concomitant administration of Radix Hydrastis with drugs metabolized via cytochrome P450 may therefore affect the metabolism of such drugs (*46*).

Carcinogenesis, mutagenesis, impairment of fertility

The genotoxic effects of berberine in prokaryotic cells were assessed in the SOS-ChromoTest in *Saccharomyces cerevisiae* (*47*). No genotoxic activity with or without metabolic activation was observed, and no cytotoxic or mutagenic effects were seen under nongrowth conditions. However, in dividing cells, the alkaloid induced cytotoxic and cytostatic effects in proficient and repair-deficient *Saccharomyces cerevisiae*. In dividing cells, the induction of frameshift and mitochondrial mutations and crossing over showed that the compound is not a potent mutagen (*47*).

Pregnancy: non-teratogenic effects

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended during pregnancy.

Nursing mothers

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended in nursing mothers.

Paediatric use

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended in children.

Other precautions

No information available on precautions concerning drug and laboratory test interactions; or teratogenic effects during pregnancy.

Dosage forms

Dried rhizomes and roots, dried extracts, fluidextracts, and tinctures (*1, 11*). Store dried rhizomes and roots in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Daily dose: dried rhizomes and roots 0.5–1.0 g three times, or by decoction; liquid extract 1:1 in 60% ethanol, 0.3–1.0 ml three times; tincture 1:10 in 60% ethanol, 2–4 ml three times (*1*).

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Radix Ipecacuanhae

Definition

Radix Ipecacuanhae consists of the dried roots and rhizomes of *Cephaelis ipecacuanha* (Brot.) A. Rich., of *C. acuminata* (Benth.) Karst. (Rubiaceae), or of a mixture of both species (*1–9*).

Synonyms

Cephaelis ipecacuanha: Callicocca ipecacuanha Brot., *Cephaelis emetica* Pers., *Evea ipecacuanha* (Brot.) Standl., *Ipecacuanha officinalis* (Brot.) Farw., *Psychotria emetica* Vell., *P. ipecacuanha* (Brot.) Muell. Arg. (also Stokes), *Uragoga emetica* Baill., *U. ipecacuanha* (Willd.) Baill. (*3, 8, 10*).

Cephaelis acuminata: Psychotria acuminata Benth., *Uragoga acuminata* (Benth.) O. Kuntze, *U. granatensis* Baill. (*3, 10*).

Selected vernacular names

Ark ad dhahab, Brazilian ipecac (= *Cephaelis ipecacuanha* (Brot.) A. Rich.), Cartagena ipecac (= *Cephaelis acuminata* (Benth.) Karst.), Cartagena ipecacuanha, ipeca, ipecac, ipecacuanha, ipecacuana, jalab, Kopfbeere, matto grosso, mayasilotu, Nicaragua ipecac (= *Cephaelis acuminata* (Benth.) Karst.), poaia, raicilla, raizcilla, Rio ipecac (= *Cephaelis ipecacuanha* (Brot.) A. Rich.), togeun (*1, 3, 5, 10–13*).

Geographical distribution

Indigenous to Brazil and Central America (*3, 8, 14*).

Description

Cephaelis ipecacuanha: A low straggling shrub. Underground portion consists of a slender rhizome bearing annulated wiry roots and slender smooth roots. Rhizome arches upwards and becomes continuous with a short, green, aerial stem bearing a few opposite, petiolate, stipulate, entire, obovate leaves. Flowers small, white and capitate, occurring in the leaf

axils; corolla infundibuliform. Fruits are clusters of dark purple berries, each containing two plano-convex seeds (*15*).

Cephaelis acuminata: Resembles *Cephaelis ipecacuanha*, but has a root with less pronounced annulations (*15*).

Plant material of interest: dried roots and rhizomes

General appearance

Cephaelis ipecacuanha: Roots somewhat tortuous pieces, from dark reddish-brown to very dark brown, seldom more than 15 cm long or 6 mm thick, closely annulated externally, completely encircled by rounded ridges; fracture short in the bark and splintery in the wood. Transversely cut surface shows a wide greyish bark and a small uniformly dense wood. Rhizome in short lengths usually attached to roots, cylindrical, up to 2 mm in diameter, finely wrinkled longitudinally, with pith occupying approximately one-sixth of the diameter (*4, 5*).

Cephaelis acuminata: Roots generally resemble those of *Cephaelis ipecacuanha* but differ in the following particulars: often up to 9 mm thick; external surface greyish-brown or reddish-brown with transverse ridges, 0.5–1.0 mm wide, at intervals of usually 1–3 mm, extending about halfway round the circumference and fading at the extremities into the general surface level (*4, 5*).

Organoleptic properties

Odour: slight, irritating, sternutatory; taste: bitter, nauseous, unpleasant (*1–4, 6, 9*).

Microscopic characteristics

Cephaelis ipecacuanha: Root cork narrow, dark brown, formed of several layers of thin-walled cells, usually with brown granular contents; phelloderm cortex parenchymatous, containing numerous starch granules, and scattered idioblasts with bundles of calcium oxalate raphides; phloem very narrow with short wedges of sieve tissues, but no fibres or sclereids; xylem wholly lignified consisting of tracheids, with rounded ends and linear pits, narrow vessels with rounded lateral perforations near the ends, substitute fibres with oblique, slit-like pits containing starch grains, a few lignified fibres, and traversed by medullary rays, one or two cells wide, lignified, containing starch; primary xylem, three-arched at the centre. Rhizome cork has a narrow parenchymatous cortex; endodermis, pericycle with thick-walled, pitted and elongated rectangular sclereids; phloem with fibres; xylem radiating with fibres having linear pits and spiral

vessels in the protoxylem and pith with isodiametric, lignified, thin-walled cells. Starch granules, rarely simple, mostly compound with two to eight components; individual granules oval, rounded or muller-shaped, 4–10 µm but can be up to 15 µm in diameter (*1, 3, 4*).

Cephaelis acuminata: Similar to *C. ipecacuanha*, but starch granules are larger, up to 22 µm in diameter (*4*).

Powdered plant material

Cephaelis ipecacuanha: Greyish-brown to light brown; numerous fragments of thin-walled parenchymatous cells filled with starch granules, scattered cells with bundles of raphides of calcium oxalate; a few brown fragments of cork; a few fragments of wood showing tracheids, tracheidal-vessels of fibrous cells with starch granules; calcium oxalate raphides, 20–80 µm long scattered throughout the powder, sometimes in fragments; numerous starch granules, simple or mostly compound with two to eight components; individual granules oval, rounded or muller-shaped, up to 15 µm in diameter. A few vessels and sclereids, and occasional phloem fibres from the rhizome (*1, 3*).

Cephaelis acuminata: Similar to *Cephaelis ipecacuanha*, but starch grain up to 22 µm in diameter (*1, 3*).

General identity tests

Macroscopic and microscopic examinations (*1–6, 8, 9*), microchemical tests (*1–3, 6, 8, 9*), and thin-layer chromatography (*4, 5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Foreign organic matter

Not more than 2% (*5, 9*).

Total ash

Not more than 5% (*2, 5, 6*).

Acid-insoluble ash

Not more than 3% (*2, 4, 5, 6*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*5*). For other pesticides, see the *European pharmacopoeia* (*5*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*17*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

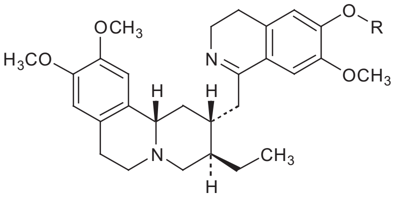
Other purity tests
Chemical, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 2% of total alkaloids calculated as emetine, determined by titration (*1–5, 9*). Assay for emetine and cephaeline by column chromatography plus spectrophotometry (*9*). A high-performance liquid chromatography method is also available.

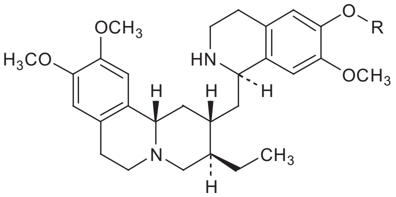
Major chemical constituents
The major active constituents are isoquinoline alkaloids (1.8–4.0%), with emetine and cephaeline accounting for up to 98% of the alkaloids present. Content in *Cephaelis ipecacuanha*: emetine 60–70%, cephaeline 30–40%; in *Cephaelis acuminata*: emetine 30–50%, cephaeline 50–70%. A 30-ml dose of ipecac syrup contains approximately 24 mg of emetine and 31 mg of cephaeline (*18*). Other alkaloids of note are psychotrine, *O*-methylpsychotrine and ipecoside (*10, 13, 14, 19*). Representative structures of the alkaloids are presented below.

Medicinal uses
Uses supported by clinical data
A syrup made from the roots is used as an emetic, to empty the stomach in cases of poison ingestion (*20*).

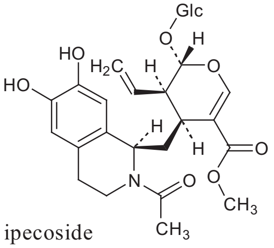
Uses described in pharmacopoeias and well established documents
See Uses supported by clinical data (*20*).



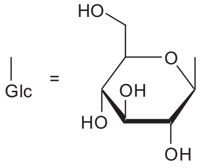
psychotrine R = H
O-methylpsychotrine R = CH_3



cephaeline R = H
emetine R = CH_3



ipecoside



β-D-glucopyranosyl

Uses described in traditional medicine

Treatment of parasites, the common cold and diarrhoea (*13*). Also to stimulate uterine contractions and induce abortion (*21*).

Pharmacology

Experimental pharmacology

In vivo studies

Experimental studies in animals are primarily limited to various investigations in dogs. In these studies most of the animals were not anaesthetized; however, some were premedicated to prevent spontaneous vomiting. The efficacy of a syrup made from Radix Ipecacuanhae to induce emesis was investigated in fasting dogs, pretreated by intramuscular or intravenous administration of 25.0 mg of chlorpromazine, 25.0 mg of promethazine or 37.5–50.0 mg of promethazine to prevent spontaneous vomiting. The pretreatments were administered 30 minutes prior to the oral administration of 500.0 mg/kg body weight (bw) of sodium salicylate in tablet form. The animals were then given 25.0 ml of a syrup made from the roots. When the syrup was administered orally within 30 minutes of the sodium salicylate dose, almost 50% of the salicylate was recovered. Administration after 30 minutes reduced recovery to 35.9% (*22*). In dogs, oral administration of 5 g of barium sulfate in suspension as a marker was followed by intragastric administration of 1.5 ml/kg bw of a syrup made from the roots at 0, 30 or 60 minutes. Mean time to emesis was 46 minutes, and recovery of the barium was 62%, 44% and 31%, respectively in the three groups (*23*). Fasting puppies were given two gelatin capsules of

barium sulfate (1.0 g) as a marker, followed after 20 minutes by intragastric administration of 15–30.0 ml of the syrup. Mean time to emesis was 29 minutes. Only three of the six dogs vomited and emesis resulted in a mean recovery of 19% (*24*). Paracetamol poisoning was induced in fasting dogs; drug emesis was 42.2% following intragastric administration of 20.0 ml of a syrup made from the roots given 10 minutes after the paracetamol dose (*25*).

Clinical pharmacology

In a randomized controlled crossover study, 10 fasting healthy volunteers received oral doses of paracetamol (3.0 g total dose), followed after 60 minutes by oral administration of 30.0 ml of a syrup prepared from the roots and 240.0 ml of water. Mean time to first emesis was 25.5 minutes. The 8-hour area under the curve for the paracetamol blood level in the syrup group was 21% lower than that for the control group (*26*).

Oral administration of 30.0 ml of a syrup prepared from the roots and 250.0 ml of water to 10 volunteers 60 minutes after the oral ingestion of 5.0 g of ampicillin prevented approximately 38% of the drug from being absorbed ($P < 0.01$). Mean time to emesis was 16 minutes (*27*).

In a randomized controlled crossover study, 10 of 12 volunteers were each given 24 acetylsalicylic acid tablets (81.0 mg/tablet) with 240.0 ml of water following a 12-hour fast. The two control subjects received no treatment. After 60 minutes, the volunteers were given 30.0 ml of a syrup prepared from the roots and 240.0 ml water; the dose was repeated in three subjects who did not vomit within 30 minutes of the initial dose. Time to emesis was approximately 30 minutes. Urine was collected for 48 hours. The proportion of ingested salicylate recovered in the urine was 96.3% for the control group and 70.2% for the treatment group ($P < 0.01$) (*28*).

In a randomized controlled crossover study 12 fasting adults were given 20 acetylsalicylic acid tablets (75.0 mg/tablet) with 200.0 ml of water followed by 30.0 ml of a syrup prepared from the roots 60 minutes later or no further treatment (control group). The mean percentage of ingested salicylate recovered in the urine was 60.3% for the control group and 55.6% for the treatment group ($P < 0.025$) (*29*).

In a controlled crossover study, oral administration of 1.0 g of paracetamol, 500.0 mg of tetracycline and 350.0 mg of a long-acting aminophylline preparation to six fasting adults was followed by oral administration of 20.0 ml of a syrup prepared from the roots and 300.0 ml of water administered either 5 minutes or 30 minutes later. Timed blood samples were collected over a 24-hour period. Mean time to onset of emesis was 14.3 minutes. For paracetamol, the mean peak serum concentra-

tion was reduced significantly ($P < 0.01$) to 4.4 mg/l after the administration of the syrup after 5 minutes compared with 14.9 mg/l in controls. Under these conditions the mean area under the curve was 35% of that in controls ($P < 0.01$). No statistically significant reduction in the mean peak serum concentration or mean area under the curve was observed when the syrup was given after 30 minutes. For tetracycline, the mean peak serum concentration and area under the curve were reduced significantly ($P < 0.01$) in both the 5- and 30-minute treatment groups. For aminophylline, the mean peak serum concentration was only reduced significantly ($P < 0.05$) in the 5-minute group (*30*).

In a randomized, controlled crossover trial, oral administration of 20.0 mg of metoclopramide to seven fasted adults was followed 60 minutes later by oral administration of 400.0 mg of cimetidine and 10.0 mg of pindolol, and after a further 5 minutes by 400.0 ml of water or 20.0 ml of a syrup prepared from Radix Ipecacuanhae and 400.0 ml of water. Six of the seven subjects vomited, with a mean time delay of 17 minutes. The syrup reduced the absorption of both cimetidine (25% of that in controls) and pindolol (40% of that in controls) as measured by mean peak serum concentrations (*31*).

In three investigations, markers were administered to emergency department patients presenting with potentially toxic ingestions, and recovery of the marker after syrup-induced emesis was measured. In one study, 14 children received an oral dose of 1.0 g of magnesium hydroxide prior to oral administration of 20.0 ml of a syrup prepared from the roots. Mean time to emesis was 15 minutes (range 5–41 minutes) and mean recovery of magnesium hydroxide was 28% (*32*). In a similar study, 100 mg of liquid thiamine mixed with 30 ml of a syrup prepared from the roots was administered to 51 subjects (*33*). Mean time to emesis was 21 minutes and mean recovery of thiamine was 50%. In a randomized, controlled, single-blind study, barium-impregnated 3-mm polythene pellets were administered with water and 30.0 ml of a syrup prepared from the roots to 20 patients. Time to emesis was 5–20 minutes. Abdominal X-rays were performed 15–80 minutes after ingestion of the pellets. In the syrup group, 39.3% of the ingested pellets had moved into the small bowel compared with 16.3% in the control group (*34*).

In a controlled, randomized prospective study, 592 acute oral drug overdose patients were evaluated to determine whether a syrup prepared from Radix Ipecacuanhae and activated charcoal or lavage and activated charcoal were superior to activated charcoal alone. The induction of emesis by the syrup before administration of activated charcoal and a cathartic ($n = 214$) did not significantly alter the clinical outcome of patients who were awake and alert on presentation compared with those who re-

ceived activated charcoal and a cathartic without the syrup (*n* = 262). The investigators concluded that induction of emesis in acutely poisoned patients who were alert and awake was of no benefit, even when performed less than 60 minutes after a toxic ingestion (*35*).

A prospective study was conducted to assess the effect of gastric emptying and activated charcoal upon clinical outcome in acutely self-poisoned patients. Presumed overdose patients (*n* = 808) were treated using an alternate-day protocol based on a 10-question cognitive function examination and presenting vital-sign parameters. Asymptomatic patients (*n* = 451) did not undergo gastric emptying. Activated charcoal was administered to asymptomatic patients only on even days. Gastric emptying in the remaining symptomatic patients (*n* = 357) was performed only on even days. On emptying days, alert patients had ipecac-induced emesis while obtunded patients underwent gastric lavage. Activated charcoal therapy followed gastric emptying. On non-emptying days, symptomatic patients were treated only with activated charcoal. No clinical deterioration occurred in the asymptomatic patients treated without gastric emptying. Use of activated charcoal did not alter outcome measures in asymptomatic patients. Gastric emptying procedures in symptomatic patients did not significantly alter the duration of stay in the emergency department, mean duration of intubation, or mean duration of stay in the intensive care unit. Gastric lavage was associated with a higher prevalence of medical intensive care unit admissions ($P = 0.0001$) and aspiration pneumonia ($P = 0.0001$). The data support the management of selected acute overdose patients without gastric emptying and fail to show a benefit from treatment with activated charcoal in asymptomatic overdose patients (*36*).

A prospective, randomized, unblinded, controlled trial was conducted to determine the effect of a syrup of the roots on the time to administration and duration of retention of activated charcoal, and on total duration of emergency department stay. The study involved 70 children less than 6 years old, who presented with mild–moderate acute oral poison ingestions. The children were divided into two groups, group 1 received the syrup before activated charcoal and group 2 received only activated charcoal. Duration from arrival to administration of activated charcoal was significantly longer in group 1 (2.6 h compared with 0.9 h, $P < 0.0001$) and group 1 children were significantly more likely to vomit activated charcoal (18 of 32 compared with 6 of 38, $P < 0.001$). Patients receiving the syrup who were subsequently discharged spent significantly more time in the emergency department than those receiving only activated charcoal (4.1 ± 0.2 h compared with 3.4 ± 0.2 h, $P < 0.05$). It was concluded that administration of the syrup delays the administration of activated charcoal, hinders its retention, and

prolongs the emergency department stay in paediatric ingestion patients (*37*). In a prospective randomized controlled trial, 876 patients were assessed on presentation to an emergency room after ingestion of a toxic substance. On odd-numbered days, the patients received 30–50 ml of syrup prepared from the roots followed by 200 ml of water, or gastric lavage followed by activated charcoal. On even-numbered days, no gastric emptying was performed and patients received 50 g of activated charcoal alone. No significant differences between the treatments were observed; syrup plus activated charcoal was not superior to activated charcoal alone (*38*).

A comparison study assessed the difference between early and late administration of ipecac syrup on paracetamol plasma concentrations. A total of 50 children under the age of 5 years with accidental ingestion of 150.0 mg/kg bw of paracetamol received ipecac syrup within 4 hours of ingestion: 23 received ipecac at home (mean time to administration 26 minutes after paracetamol ingestion) and had measured plasma paracetamol concentrations of 23.0 mg/l; 27 children received ipecac syrup elsewhere (i.e. not at home; mean time to administration, 83 min) and had measured plasma paracetamol concentrations of 44.0 mg/l. The investigators concluded that the shorter the time between ingestion of paracetamol and the administration of ipecac, the more effective ipecac was in reducing plasma paracetamol concentrations (*39*).

The rates of absorption and elimination of emetine and cephaeline from a syrup prepared from the roots were investigated in 10 healthy adults. Volunteers received an oral dose of 30 ml of the syrup and urine and blood samples were collected up to 180 minutes following ingestion. In all subjects emetine and cephaeline were detected in the blood 5–10 minutes after dosing, with maximum concentrations observed after 20 minutes. The mean areas under the curve were similar for both compounds. Less than 0.15% of the administered emetine and cephaeline doses was recovered in the urine at 3 hours. There was no relation between peak vomiting episodes and blood levels of emetine and cephaeline. At 3 hours neither alkaloid was detectable in the blood (*40*).

The roots act as an emetic because of their local irritant effect on the digestive tract and its effect on the chemoreceptor trigger zone in the area postrema of the medulla (*41*). Charcoal should not be administered with syrup prepared from the roots, because charcoal can absorb the syrup and reduce the emetic effect.

Adverse reactions

Large doses of Radix Ipecacuanhae have an irritant effect on the gastrointestinal tract, and may induce persistent bloody vomiting or diarrhoea

(*20*). Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which may occur if vomiting is not induced, may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, in combination with dehydration, may cause vasomotor collapse followed by death. Chronic abuse of the roots to induce vomiting in eating disorders has been implicated in the diagnosis of cardiotoxicity and myopathy due to the accumulation of emetine (*20*). Adverse effects of repeated vomiting, such as metabolic complications, aspiration pneumonitis, parotid enlargement, dental abnormalities, and oesophagitis or haematemesis due to mucosal lacerations may be observed (*20*). Cardiovascular toxicity, manifesting as muscle weakness, hypotension, palpitations and arrhythmias, may occur (*42, 43*). Death was reported for one subject who had ingested 90–120 ml of a syrup prepared from the roots per day for 3 months (*44*).

Prolonged vomiting has been reported in 17% of patients given the roots for the treatment of poisoning, which may lead to gastric rupture, Mallory-Weiss lesions of the oesophagogastric junction, cerebrovascular events, pneumomediastinum and pneumoperitoneum (*45*).

Allergy to the roots was reported after inhalation of powdered roots, characterized by rhinitis, conjunctivitis and chest tightness (*46*).

There have been a number of deaths reported in small children due to an overdose owing to the substitution of 10.0–60.0 ml of a fluidextract of the roots for a syrup prepared from the roots (*18, 47, 48*). It is believed that the fluidextract was mistaken for the syrup. The fluidextract is 14 times more potent than the syrup (*20*).

Other adverse reactions to the roots include severe diarrhoea, nausea and abdominal cramps (*49*).

Contraindications

While emesis is usually indicated after poisoning resulting from oral ingestion of most chemicals, emesis induced by Radix Ipecacuanhae is contraindicated in the following specific situations: following ingestion of a corrosive poison, such as strong acid or alkali; when airway-protective reflexes are compromised, for example in patients who are comatose or in a state of stupor or delirium; following ingestion of a central nervous system stimulant, when vomiting may induce convulsions; in cases of strychnine poisoning; or following ingestion of a petroleum distillate (*18, 41*). Radix Ipecacuanhae has been used as an abortifacient in traditional medicine and its use is therefore contraindicated during pregnancy. See also Warnings, and Precautions.

Warnings

Numerous deaths have occurred owing to the administration of a fluidextract of Radix Ipecacuanhae instead of a syrup prepared from the roots. The fluidextract is 14 times stronger than the syrup and should never be administered as a substitute for the syrup.

Precautions

General

Radix Ipecacuanhae should not be used as an emetic in patients whose condition increases the risk of aspiration or in patients who have taken substances that are corrosive or petroleum products that may be dangerous if aspirated (*20*). The roots should not be given to patients in shock, at risk of seizure, or with cardiovascular disorders (*20*).

Drug interactions

The emetic action of the roots may be delayed or diminished if given with or after charcoal. Concomitant administration of milk was believed to reduce the efficiency of emesis induced by the roots. However, no significant differences in the time to onset of vomiting, the duration of vomiting, or the number of episodes were observed in 250 children who were given a syrup prepared from the roots with milk compared with 250 children given the syrup with clear fluids (*50*).

Decreases in the absorption of paracetamol, tetracycline and aminophylline were observed after concomitant administration of 20.0 ml of an aqueous extract of the roots (*30, 51*).

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the roots, 50.0 µg/ml, was not mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 (*52*). The mutagenicity of a fluidextract of the roots was evaluated in the *Salmonella*/microsome assay, the chromosomal aberration test in cultured Chinese hamster lung cells and the mouse bone marrow micronucleus test (oral administration). No mutagenic effects were observed (*53*).

Pregnancy: non-teratogenic effects

See Contraindications.

Paediatric use

Do not exceed recommended doses. Do not give the fluidextract to children. For children up to 6 months of age, the syrup should only be administered under the supervision of a physician (*18*).

Other precautions

No information available on precautions concerning drug and laboratory test interactions; teratogenic effects during pregnancy; or nursing mothers.

Dosage forms

Dried roots and rhizomes, liquid extracts, fluidextract, syrup and tincture (*20*). Dried roots and rhizomes should be stored in a tightly sealed container, protected from light (*20*).

Posology

(Unless otherwise indicated)

As an emetic in cases of poisoning other than corrosive or petroleum-based products. Doses should be followed by ingestion of copious volumes of water. Doses may be repeated once, 20–30 minutes after the initial administration, if emesis has not occurred (*20*). Adults: Ipecac Syrup, 15–30 ml (21–42 mg total alkaloids). Children: 6 months–1 year, 7–14 mg of total alkaloids (5–10 ml) of Ipecac Syrup; older children, 21 mg of total alkaloids represented in 15 ml Ipecac Syrup (*9*).

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Aetheroleum Lavandulae

Definition

Aetheroleum Lavandulae consists of the essential oil obtained by steam distillation from the fresh flowering tops of *Lavandula angustifolia* Mill. or of *L. intermedia* Loisel (Lamiaceae) (*1–4*).

Synonyms

Lavandula officinalis Chaix, *L. spica* Loisel., *L. vera* DC., *L. vulgaris* Lam. (*5–8*). Lamiaceae are also known as Labiatae. In most formularies and older reference books, *Lavandula officinalis* Chaix is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Lavendula angustifolia* Mill. is the legitimate name for the species (*8, 9*).

Selected vernacular names

Al birri, alhucema, arva neh, aspic, broad-leaved lavenda, common lavender, Echter Lavendel, English lavender, espi, espic, espliego commún, firigla, frigous, garden lavendar, grando, hanan, hanene, hzama, khazama, khirii, khouzamaa, khouzami, khuzama, khuzama fassiya, khuzama zerqua, Kleiner Speik, Lavanda, lavande, lavande femelle, lavande véritable, lavando, lavandula vraie, Lavendel, lavender, lawanda, lófinda, ostoghodous, postokhodous, spigandos, true lavender (*6, 8–14*).

Geographical distribution

Indigenous to the northern Mediterranean region. Cultivated in southern Europe, and in Bulgaria, Russian Federation, United States of America, and the former Yugoslavia (*8, 15*).

Description

An aromatic shrub, 1–2 m high. Branches grey-brown to dark brown with long flowering and short leafy shoots, bark longitudinally peeling. Leaves clustered on leafy shoots, widely spaced on flowering shoots; petiole very short; blade linear-lanceolate to linear, 17 mm long, 2 mm wide

on leafy shoots, 2–6 cm long, 3–6 mm wide on flowering shoots; grey stellate tomentose, base attenuate, margin entire, revolute, apex obtuse. Inflorescence a crowded, interrupted or nearly continuous spike, 2–8 cm long; verticillasters numerous, with 6–10 flowers, upper ones densely crowded; peduncle about three times longer than the spike; bracts papery, rhombic-ovate, 3–8 mm long, rust coloured when dry; bracteoles absent or up to 2.5 mm long, pedicel 1.0–1.5 mm long; calyx 4–7 mm long, densely grey stellate tomentose outside, with 13 longitudinal ribs, upper lip entire, appendage obcordate, lower lip four-toothed; corolla 10–12 mm long, blue, base subglabrous, throat and limb glandular hairy, upper lips straight, lower lips spreading. Nutlets narrowly cylindrical (*8*).

Plant material of interest: essential oil

General appearance

A clear colourless or pale yellow liquid, miscible with 90% alcohol, ether and fatty oils (*1–4*).

Organoleptic properties

Odour: characteristic, fragrant, aromatic; taste: aromatic, slightly bitter (*1, 3*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Macroscopic examinations (*1, 3, 4*); refractive index, specific gravity and optical rotation measurements (*2*); thin-layer chromatography for the presence of linalyl acetate and linalool (*4*), and gas chromatography (*4*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*16*).

Chemical

Relative density 0.878–0.892 (*4*). Refractive index 1.455–1.466 (*4*). Optical rotation -12.5–7° (*4*). Acid value not more than 1.0 (*4*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*17*). For other pesticides, see the *European pharmacopoeia* (*17*), and the WHO guidelines on quality control methods for medicinal plants (*16*) and pesticide residues (*18*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*16*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*16*) for the analysis of radioactive isotopes.

Other purity tests

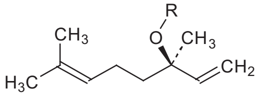
Tests for foreign organic matter, total ash and acid-insoluble ash not applicable. Tests for water-soluble extractive and acid-soluble extractive to be established in accordance with national requirements.

Chemical assays

Official analysis by gas chromatography shows the following composition: limonene, cineole, 3-octanone, camphor, linalool, linalyl acetate, terpinen-4-ol, lavandulyl acetate, lavandulol, α-terpineol (*4*).

Major chemical constituents

Contains: linalyl acetate (25–46%), linalool (20–45%), terpinen-4-ol (1.2–6.0%), lavendulyl acetate (> 1.0%), 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol) (< 2.5%), 3-octanone (< 2.5%), camphor (< 1.2%), limonene (< 1.0%), and α-terpineol (< 2.0%) (*4*). The structures of linalyl acetate and linalool are presented below.



and enantiomer

linalool R = H

linalyl acetate R = CO-CH3

Medicinal uses

Uses supported by clinical data

Inhalation therapy for symptomatic treatment of anxiety, restlessness and to induce relaxation (*19–22*). Externally in balneotherapy for the treatment of circulation disorders (*23*).

Uses described in pharmacopoeias and well established documents
Symptomatic treatment of insomnia, and as a carminative for the treatment of gastrointestinal disorders of nervous origin (*15, 24*).

Uses described in traditional medicine
Orally as a cholagogue, diuretic and emmenagogue; externally for the treatment of burns, diarrhoea, headaches, sore throats and wounds (*15*).

Pharmacology
Experimental pharmacology
Anaesthetic activity
In vitro, the essential oil, linalyl acetate and linalool, 0.01–10.0 μg/ml in the bath medium, reduced electrically-evoked contractions of a rat phrenic-hemidiaphragm (*25*). In the rabbit conjunctiva test in vivo, administration of an aqueous solution of the essential oil, linalyl acetate or linalool, 30.0–2500.0 μg/ml, into the conjunctival sac increased the number of stimuli needed to provoke the reflex (*25*).

Anticonvulsant and sedative activities
Intraperitoneal administration of 2.5 g/kg body weight (bw) of linalool to rodents protected against convulsions induced by pentylenetetrazole, picrotoxin and electroshock (*26, 27*). In mice, intraperitoneal administration of 2.5 g/kg bw of linalool interfered with glutamate function and delayed *N*-methyl-D-aspartate-induced convulsions (*28*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes, suggesting interference of glutamatergic transmission. The effects of linalool on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes were investigated. Linalool reduced potassium-stimulated glutamate release (*29*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission system.

Anti-inflammatory activity
The effect of Aetheroleum Lavandulae on immediate-type allergic reactions was investigated in vitro and in vivo. External and intradermal administration of aqueous dilutions of the essential oil, 1:500, 1:100, 1:10, 1:1 and 1:0, to mice inhibited mast cell-dependent ear oedema induced by compound 48/80 (*30*). Administration of the essential oil (same dose range) to rats inhibited passive cutaneous anaphylaxis induced by anti-dinitrophenyl (DNP) IgE, compound 48/80-induced histamine release and anti-DNP IgE-induced tumour necrosis factor-α secretion from peritoneal mast cells (*30*). Inhalation of 0.3 ml of the essential oil inhibited

thromboxane B_2 release induced by arachidonic acid in mice, suggesting an anti-inflammatory effect (*31*).

Antimicrobial and acaricidal activities
The undiluted essential oil inhibited the growth of *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pneumoniae* in vitro (*32, 33*). The undiluted essential oil, 10.0 µl/disc, inhibited the growth of *Mycobacterium chelonae, M. fortuitum*, *M. kansasii*, *M. marinum* and *M. scrofulaceum* (*34*). The undiluted essential oil inhibited the growth of filamentous fungi in vitro (*35*). The essential oil, linalool, linalyl acetate and camphor had miticidal activity against *Psoroptes cuniculi* in rabbits (*36*).

Antispasmodic activity
Addition of the essential oil to the bath medium, 0.02 mg/ml and 0.2 mg/ml, reduced the twitching response and relaxed the muscle tone of rat phrenic nerve diaphragm preparations in vitro (*37*). The antispasmodic activity of the essential oil and linalool was mediated through the cyclic adenosine monophosphate signal transduction system, determined using a guinea-pig ileum smooth muscle preparation (*38*).

Central nervous system depressant effects
Inhalation of the essential oil (dose not specified) by mice reduced caffeine-induced hyperactivity, which was correlated with linalool serum levels (*39*). Intragastric administration of the essential oil (dose not specified) to rats produced anxiolytic effects and prolonged pentobarbital sleeping time (*40*).

Intragastric administration of 1.6 g/kg bw of the essential oil increased the lever-pressing response rate during the alarm phase of the Geller-type conflict test in animals, suggesting that the oil had an anticonflict effect similar to that of diazepam (*41*). Intragastric administration of 25.0 ml/kg bw of the essential oil, diluted 60 times in olive oil, prolonged pentobarbital sleeping times in mice (*42*). Inhalation of 0.3 ml of the essential oil inhibited strychnine-induced convulsions in mice (*31*).

Clinical pharmacology

Anxiolytic activity
In a comparison clinical trial without placebo, 40 healthy volunteers received aromatherapy (inhalation) with Aetheroleum Lavandulae or essential oil of rosemary (*Rosmarinus officinalis*) and were then asked to perform some simple mathematical computations. In the group treated with Aetheroleum Lavandulae, the electroencephalogram showed an increase in beta power, suggesting increased drowsiness. The subjects treated with this

oil also reported feeling less depressed and more relaxed, and performed the mathematical computation more accurately after the therapy (*20*).

In an uncontrolled trial in 13 healthy volunteers, inhalation of Aetheroleum Lavandulae significantly ($P < 0.001$) decreased alpha-1 frequencies (8–10 Hertz) shortly after inhalation, and the subjects reported feeling "comfortable" in a subjective evaluation of the treatment (*22*).

In a randomized study involving 122 patients admitted to a general intensive care unit, patients received either massage, aromatherapy with the oil (1% essential oil in grapeseed oil; 1–3 treatments over a 5-day period) or a period of rest to assess the efficacy of these factors on the stress response and anxiety. No difference between the three therapies was observed for the stress response. However, patients treated with the oil aromatherapy reported improvements in mood and a reduction of anxiety (*19*).

In 14 patients on chronic haemodialysis, inhalation of the essential oil over a one-week period decreased the mean score in the Hamilton anxiety rating scale compared with controls undergoing inhalation of odourless substances (*21*).

Analgesic activity

In a preliminary clinical trial without controls, addition of six drops of the essential oil to bath water daily for 10 days following childbirth did not reduce the incidence of perineal discomfort except for the period between days 3 and 5 postpartum (*43*). In a single-blind randomized clinical trial in 635 postpartum women, subjects were given pure Aetheroleum Lavandulae, synthetic lavender oil or an inert oil to use as a bath additive for 10 days postpartum. No difference between the therapies in the reduction of perineal discomfort was observed (*44*).

Cardiovascular effects

In a randomized crossover controlled study, healthy volunteers (number not specified) sat with their feet soaking in hot water for 10 minutes with or without the addition of the oil. Electrocardiogram, fingertip blood flow and respiration rate measurements indicated that treatment with the oil increased parasympathetic nerve activity and increased blood flow but had no effects on heart or respiratory rates (*23*).

Adverse reactions

Allergic contact dermatitis has been reported in patients previously exposed to the essential oil (*45–49*).

Contraindications

Aetheroleum Lavandulae is contraindicated in cases of known allergy to the plant material. Owing to its traditional use as an emmenagogue and abortifacient, the essential oil should not be used internally during pregnancy (*50–52*).

Warnings

Essential oils should be used with caution in children. Keep out of the reach of children.

Precautions

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to a lack of safety data, the essential oil should be administered internally only under the supervision of a health-care provider.

Paediatric use

Owing to a lack of safety data, the essential oil should be administered internally only under the supervision of a health-care provider.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; or teratogenic effects during pregnancy.

Dosage forms

Essential oil (*15*). Store in a well-closed container, in a cool, dry place, protected from light (*4*).

Posology

(Unless otherwise indicated)

Essential oil by inhalation, 0.06–0.2 ml three times per day (*7*); internally, 1–4 drops (approximately 20–80.0 mg) on a sugar cube per day (*24*).

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Flos Lavandulae

Definition

Flos Lavandulae consists of the dried flowers of *Lavandula angustifolia* Mill. (Lamiaceae) (*1–3*).

Synonyms

Lavandula officinalis Chaix, *L. spica* Loisel., *L. vera* DC, *L. vulgaris* Lam. (*1, 4, 5*). Lamiaceae are also known as Labiatae. In most formularies and older reference books, *Lavandula officinalis* Chaix is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Lavandula angustifolia* Mill. is the legitimate name for the species (*5, 6*).

Selected vernacular names

Al birri, alhucema, arva neh, aspic, broad-leaved lavenda, common lavender, Echter Lavendel, English lavender, espi, espic, espliego commún, firigla, frigous, garden lavendar, grando, hanan, hanene, hzama, khazama, khirii, khouzamaa, khouzami, khuzama, khuzama fassiya, khuzama zerqua, Kleiner Speik, Lavanda, lavande, lavande femelle, lavande véritable, lavando, lavandula vraie, Lavendel, lavender, lawanda, lófinda, ostoghodous, postokhodous, spigandos, true lavender (*1, 2, 5–9*).

Geographical distribution

Indigenous to the northern Mediterranean region. Cultivated in southern Europe and in Bulgaria, Russian Federation, United States of America and the former Yugoslavia (*5, 10*).

Description

An aromatic shrub, 1–2 m high. Branches grey-brown to dark brown with long flowering and short leafy shoots, bark longitudinally peeling. Leaves clustered on leafy shoots, widely spaced on flowering shoots; petiole very short; blade linear-lanceolate to linear, 17 mm long, 2 mm wide on leafy shoots, 2–6 cm long, 3–6 mm wide on flowering shoots; grey

stellate tomentose, base attenuate, margin entire, revolute, apex obtuse. Inflorescence a crowded, interrupted or nearly continuous spike, 2–8 cm long; verticillasters numerous, with 6–10 flowers, upper ones densely crowded; peduncle about three times longer than the spike; bracts papery, rhombic-ovate, 3–8 mm long, rust coloured when dry; bracteoles absent or up to 2.5 mm long, pedicel 1.0–1.5 mm long; calyx 4–7 mm long, densely grey stellate tomentose outside, with 13 longitudinal ribs, upper lip entire, appendage obcordate, lower lip four-toothed; corolla 10–12 mm long, blue, base subglabrous, throat and limb glandular hairy, upper lips straight, lower lips spreading. Nutlets narrowly cylindrical (*5*).

Plant material of interest: dried flowers

General appearance

Consists mainly of tubular-ovoid, ribbed, bluish-grey calices with five teeth, four of which are short, while the fifth forms an oval or cordate projecting lip. Petals, much crumpled, are fused into a tube with a lower lip consisting of three small lobes and an upper lip comprising two larger erect lobes; the colour varies from deep bluish grey to a discoloured brown. Corolla contains four stamens and a superior ovary (*10*).

Organoleptic properties

Odour: fragrant, aromatic; taste: aromatic, bitter, somewhat camphoraceous (*1, 2*).

Microscopic characteristics

Calyx and corolla bear glandular hairs with a very short unicellular stalk and a head of four to eight cells, of a labiaceous type, and characteristic branching unicellular and multicellular non-glandular hairs with pointed ends and a somewhat streaked or warty cuticle. Corolla bears also, on the inner surface at the throat, characteristic glandular hairs with a unicellular, glandular head and a bicellular stalk, its basal cell being long and knotted and the other cell short and cylindrical. Anthers covered with whip-shaped, unicellular, non-glandular trichomes; pollen grains, almost rounded, with six germ pores (*1*).

Powdered plant material

Grey-blue with fragments of calyx, elongated epidermal cells with wavy anticlinal walls, and multicellular non-glandular covering trichomes. Encapsulated labiate oil glands. Corolla fragments, almost oval and slightly wavy-walled epidermal cells, labiate oil glands and branched covering hairs; unicellular glandular hairs. Pollen grains spherical to ellipsoidal, 24–30 µm in diameter, with six furrows, six germ pores and lines of pits

radiating from the poles. Leaf fragments, almost straight-walled epidermal cells, covering branched trichomes and labiate oil glands, glandular hairs with a unicellular stalk and a bicellular head (*11*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), microchemical tests (*2*), and thin-layer chromatography for the presence of linalyl acetate and linalool (*3*, *12*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 2.0% (*3*).

Total ash

Not more than 9.0% (*3*).

Acid-insoluble ash

Not more than 1.0% (*2*).

Water-soluble extractive

Not less than 18.0% (*2*).

Alcohol-soluble extractive

Not less than 12.0% (*2*).

Moisture

Not more than 10.0% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*13*).

Other purity tests

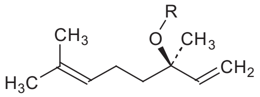
Chemical tests to be established in accordance with national requirements.

Chemical assays

Contains not less than 1.3% (v/w) essential oil determined by steam distillation (*3*).

Major chemical constituents

Contains 1.0–3.0% essential oil, of which the major constituents are linalyl acetate (30–55%) and linalool (20–50%). Other constituents include β-ocimene, 1,8-cineole (1,8-cineol, cineol, cineole, eucalyptol), camphor and caryophyllene oxide (*6, 9, 10*). The structures of linalyl acetate and linalool are presented below.



and enantiomer

linalool R = H

linalyl acetate R = CO-CH_3

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of restlessness, insomnia, and as a carminative and antispasmodic for gastrointestinal disorders of nervous origin (*10, 16*). Externally in balneotherapy for the treatment of cardiovascular disorders (*10, 16*).

Uses described in traditional medicine

As a diuretic and an emmenagogue, and for the treatment of burns, diarrhoea, headaches, sore throats and wounds (*10*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

Aqueous, chloroform, hexane and methanol extracts of Flos Lavandulae, 60.0 μg/ml, inhibited the growth of *Streptococcus pneumoniae* in vitro

(*17*). A methanol extract of the flowers inhibited the growth of *Helicobacter pylori* (the bacterium associated with peptic ulcer disease) in vitro, minimum inhibitory concentration 100.0 µg/ml (*18*).

Antioxidant activity
A 50% ethanol extract of the flowers had antioxidant activity in vitro, median effective dose 45.0 mg/ml (*19*).

Antiulcer activity
Intragastric administration of 400.0 mg/kg body weight (bw) of an 80% ethanol extract of the flowers to mice significantly ($P < 0.05$) reduced ethanol-induced gastric ulcerations by 62.9% (*20*).

Uterine stimulating activity
A hot aqueous extract of the flowers (dose not specified) stimulated uterine contractions in isolated pregnant guinea-pig uterus (*21*).

Anticonvulsant and sedative activities
Intraperitoneal administration of 2.5 g/kg bw of linalool to rodents protected against convulsions induced by pentylenetetrazole, picrotoxin and electroshock (*22, 23*). In mice, intraperitoneal administration of 2.5 g/kg bw of linalool interfered with glutamate function and delayed *N*-methyl-D-aspartate-induced convulsions (*24*). Linalool acts as a competitive antagonist of [^{3}H]-glutamate binding and as a non-competitive antagonist of [^{3}H]-dizocilpine binding in mouse cortical membranes, suggesting interference of glutamatergic transmission. The effects of linalool on [^{3}H]-glutamate uptake and release in mouse cortical synaptosomes were investigated. Linalool reduced potassium-stimulated glutamate release (*25*). These data suggest that linalool interferes with elements of the excitatory glutamatergic transmission.

Adverse reactions
No information available.

Contraindications
Flos Lavandulae is contraindicated in cases of known allergy to the plant material. Owing to their traditional use as an emmenagogue and abortifacient, the flowers should not be used during pregnancy (*21, 26*).

Warnings
No information available.

Precautions

Pregnancy: non-teratogenic effects
See Contraindications.

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic effects during pregnancy; nursing mothers; or paediatric use.

Dosage forms
Dried flowers, tablets, capsules, fluidextract, syrup, tincture and tonics (*10*). Store in a well closed container, in a cool, dry place, protected from light (*1*).

Posology
(Unless otherwise indicated)
Internally as a tea, dried flowers, 1–2 teaspoonfuls per cup, three times per day; tincture (1:5) in 60% ethanol, 2–4 ml three times per day (*11*). Externally as bath therapy, dried flowers, 20–100 g per 20 l of water (*16*).

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Strobilus Lupuli

Definition

Strobilus Lupuli consists of the dried strobiles or inflorescences of the female plants of *Humulus lupulus* L. (Cannabaceae) (*1, 2*).

Synonyms

Humulus lupulus L. var. *cordifolius* (Miq.) Maxim. in Franch. et Sav. = *H. cordifolius* Miq., *H. lupulus* L. var. *lupuloides* E. Small = *H. americanus* Nutt., *H. lupulus* L. var. *lupuloides* = *Cannabis lupulus* (L.) Scop., *H. lupulus* L. var. *brachystachyus* Zapalowicz, *H. lupulus* L. var. *neomexicanus* Nelson et Cockerell = *H. neomexicanus* (Nelson et Cockerell) Rydberg, *H. volubilis* Salisb., *H. vulgaris* Gilib., *Lupulus communis* Gaertn., *L. humulus* Mill., *L. scandens* Lam. (*3*).

Selected vernacular names

Betiguera, bine, common hops, Echter Hopfen, European hops, hachichet addinar, hoblon, hombrecillo, hop, hop vine, Hopfen, hops, houblon, houblon grimpant, houblon vulgaire, humulus, lupio, luppulo, lupol, lupulin, lupulo, pijiuha, razak, vidarria, vigne du nord, xianshema (*3–6*).

Geographical distribution

Distributed in Europe, Asia and North America. Cultivated widely in the temperate zones of the world (*5, 7*).

Description

A perennial, dioecious, twining herb, up to 6 m high. Aerial parts consist of several long, angular, rough-hairy, entwining stems bearing cordate, palmate, three-lobed, occasionally five- to seven-lobed, scabrous, dark green, stipulate leaves. Staminate flowers, with five bracts and five stamens, borne in axillary panicles. Pistillate flowers pale green, each consisting of an entire cup-like perianth and a unilocular ovary with a single ovule, and two long stigmas, borne on a leafy conical catkin. Fruits are ovate to ovate-cylindrical strobiles consisting of a flexuous rachis bearing

yellowish-green to pale brown, ovate, membranous, scaly bracts, each enclosing a brown glandular achene (*7*).

Plant material of interest: dried strobiles

General appearance

Strobiles ovoid-cylindrical or cone-like, leafy, 3–4 cm long and up to 3 cm wide, consisting of a narrow, hairy, flexuous rachis and numerous imbricated, yellowish-green to dusky yellow, obliquely ovate, membranous bracts, the base of each with numerous orange to yellowish-orange, glandular trichomes, and frequently infolded on one side, enclosing a light brown subglobular glandular achene (*7*).

Organoleptic properties

Odour: strong, characteristically aromatic, becoming valerian-like on ageing; taste: aromatic, bitter (*7*).

Microscopic characteristics

Epidermal cells of stipules and bracteoles irregularly polygonal with sinuous anticlinal walls, usually thin, occasionally slightly beaded and thickened; rare anomocytic stomata and cicatrices. Mesophyll seen in section shows small cluster crystals of calcium oxalate; glandular trichomes with a two-celled stalk and a spherical glandular head of eight cells; numerous large yellow glands, 100–250 μm in diameter, each consisting of thin-walled cells with a dome-shaped cuticle, circular in surface view and cup-shaped in side view, attached to the stipule or bracteole by a short two-celled stalk. Epicarp of fruit consists of sclerenchymatous cells, irregularly elongated, pale brown with thick walls showing numerous small pits and striations (*1*).

Powdered plant material

Greenish-yellow; fragments of bracts and bracteoles covered by polygonal, irregular epidermal cells with wavy walls; unicellular, conical, straight or curved covering trichomes with thin, smooth walls; rare anomocytic stomata; fragments of mesophyll containing small calcium oxalate cluster crystals; many characteristic orange-yellow glandular trichomes with short, bicellular, biseriate stalks, bearing a partial widening into a cup, 150–250 μm in diameter, made up of a hemispherical layer of secretory cells with a cuticle that has been detached and distended by the accumulation of oleoresinous secretions; fragments of elongated sclerenchymatous cells of the testa with thick walls showing striations and numerous pits (*2*).

General identity tests

Macroscopic and microscopic examinations (*1, 7*), and thin-layer chromatography (*1, 2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*8*).

Foreign organic matter

Not more than 2% (*1, 2*).

Total ash

Not more than 12% (*2*).

Acid-insoluble ash

Not more than 5% (*1*).

Water-soluble extractive

Not less than 10% (*2*).

Alcohol-soluble extractive

Not less than 25% in 70% (v/v) ethanol (*2*).

Loss on drying

Not more than 10% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*9*). For other pesticides, see the *European pharmacopoeia* (*9*), and the WHO guidelines on quality control methods for medicinal plants (*8*) and pesticide residues (*10*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*8*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*8*) for the analysis of radioactive isotopes.

Other purity tests

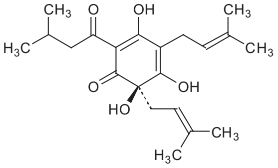
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays

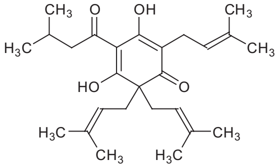
High-performance liquid chromatography for bitter substances and xanthohumol (*3*).

Major chemical constituents

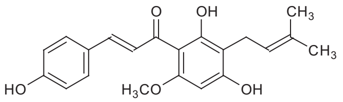
The major constituents are bitter substances (15–25%) in the resins. The resins are differentiated into hard (petroleum-ether insoluble) and soft resins. The lipophilic soft resins contain mainly α-acids (e.g. α-humulene (2,6,9-humulatriene) and related humulones) and β-acids (lupulones). The major chemical constituents of the soft resins are humulone and lupulone and their related derivatives, 2–10% and 2–6%, respectively. The hard resin contains a hydrophilic fraction, δ-resin, and a lipophilic fraction, γ-resin. The essential oil (0.3–1.0%) contains mainly monoterpenes and sesquiterpenes such as β-caryophyllene, farnesene, humulene and β-myrcene (*3, 5, 6, 11, 12*). The essential oil also contains traces of 2-methylbut-3-ene-2-ol, which increases in amount to a maximum of 0.15% after storage of the strobiles for 2 years, owing to degradation of the humulones and lupulones. Other constituents include the chalcone xanthohumol, prenylflavonoids and other flavonoids (e.g. kaempferol, rutin) and tannins (*3, 6, 13, 14*). Representative structures are presented below.



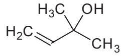
humulone



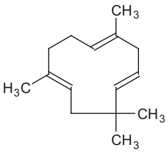
lupulone



xanthohumol



2-methylbut-3-en-2-ol



humulene

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents
As a sedative for the treatment of nervous tension and insomnia. Treatment of dyspepsia and lack of appetite (*5, 15–17*).

Uses described in traditional medicine
Treatment of abdominal cramps, anaemia, bacterial infections, dermatitis, diarrhoea, dysmenorrhoea, leukorrhoea, migraine and oedema (*6*). As an analgesic, anthelminthic, antipyretic, aphrodisiac, carminative, depurative, digestant, diuretic, diaphoretic and tonic (*6*).

Pharmacology

Experimental pharmacology

Antimicrobial activity
The essential oil of the strobiles, 2.5 µl/disc, inhibited the growth of *Staphylococcus aureus*, *Bacillus subtilis, Trichophyton interdigitale, Candida albicans* and *Escherichia coli* (*18*). Other researchers reported antimicrobial effects against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and the fungus *Trichophyton mentagrophytes* var. *interdigitale* at a concentration of 20 mg/ml, but no activity against a Gram-negative bacterium (*Escherichia coli*) or the yeast *Candida albicans* (*19*). A methanol extract of the strobiles inhibited the growth of *Helicobacter pylori*, minimum inhibitory concentration (MIC) range 63.0–130.0 µg/ml (*20*). Lupulone and humulone were isolated from the methanol extract as the active constituents. The MIC range for lupulone was estimated at 0.63–13.0 µg/ml (*20*). A decoction of the strobiles and lupulone inhibited the growth of *Mycobacterium tuberculosis*, MIC 1.0–10 µg/ml for lupulone and 7.5 µg/ml for the decoction (*17*).

The antibacterial activity of the weak acids derived from Strobilus Lupuli increases with decreasing pH of the medium. The MICs of these compounds against *Lactobacillus brevis* IFO 3960 at a pH range of 4–7 suggest that undissociated molecules are mainly responsible for the inhibition of bacterial growth (*21*).

Anti-oedema activity
External application of a methanol extract of Strobilus Lupuli to mouse ears, 2.0 mg/ear, inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced inflammation by 90% (*22*). Humulone, 1 mg/animal, inhibited ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate and ear oedema induced by arachidonic acid in mice (*23*).

Antioxidant activity

A methanol extract of the strobiles had antioxidant and radical scavenging activities in vitro (*24, 25*).

Central nervous system depressant activity

Intraperitoneal administration of 100.0 mg/kg body weight (bw) of a methanol extract of the strobiles had analgesic effects, as shown by the increased latency of licking the forepaws in the hot-plate test in mice (*26, 27*). Intraperitoneal administration of the extract also reduced spontaneous motor activity and decreased performance on an animal coordination meter (Rota-Rod) by 59% at doses above 250.0 mg/kg bw. At a dose of 250.0 mg/kg bw the extract also produced a dose-dependent increase in pentobarbital-induced sleeping time in mice (*26, 27*). However, oral doses of up to 500.0 mg/kg of an ethanol extract of the strobiles did not have any sedative effects in mice (*28*). Oral administration of a methanol extract of the strobiles, 500.0 mg/kg bw, inhibited pentylenetetrazole-induced convulsions and reduced body temperature in mice (*26, 27*). Intraperitoneal administration of 0.8 g/kg bw of the 2-methylbut-3-ene-2-ol, extracted from the essential oil of the strobiles to mice induced narcosis lasting 8 hours (*29*). Intraperitoneal administration of 206.5 mg/kg bw of 2-methylbut-3-ene-2-ol to rats caused a 50% decrease in motility (*30*).

Administration of an essential oil of the strobiles via nasogastric tube (dose not specified) induced central nervous system depression in pigeons (*31*). Intramuscular administration of an essential oil (dose not specified) to mice had unspecified sedative activity (*29*). A commercial extract (no further information available) of the strobiles, ≤2 µg/ml, bound to the γ-aminobutyric acid, the glutamate and the *N*-methyl-D-asparate receptors, as well as the chloride ion channel and glycine receptors in vitro (*32*).

Estrogenic activity

Subcutaneous administration of an aqueous or a 95% ethanol extract of the strobiles at various concentrations had estrogenic effects in mice and rats as assessed by the Allen-Doisy assay (which measures vaginal cornification in ovariectomized animals) (*33–37*). The activity was reported to be equivalent to that of 20–300 µmol/g bw of 17-β-estradiol (*33*). Using the Allen-Doisy assay, the estrogenic hormonal activity of a lipophilic extract of the strobiles was greater than that of an aqueous extract of 17-β-estradiol equivalents (1250 µg/g bw compared with 30–300 µg/g bw) (*35*). However, other investigators reported no estrogenic effects in mice following subcutaneous administration of doses of up to 51.0 mg/kg bw (*38, 39*).

Subcutaneous administration of 5.0 mg of an alcohol extract of the strobiles to rats had a luteal suppressant effect (*40*). An extract of the

strobiles (unspecified) administered to ovariectomized rats in the diet (dose not specified) bound to estrogen receptors in vitro, and increased the concentration of hepatic ceruloplasmin messenger RNA, indicating an hepatic estrogenic response (*41*).

A polyphenolic fraction isolated from an alcohol extract of the strobiles stimulated the activity of alkaline phosphatase in human endometrial cells, Ishikawa variety I in vitro (*42*). A phytoestrogen, 8-prenylnaringenin, isolated from the polyphenolic fraction, 1 nmol/l, bound to estrogen receptors isolated from rat uteri (*42*). Methanol extracts of the strobiles competitively bound to estrogen receptors-alpha and -beta from rat uteri (*43*). The extracts also induced the expression of alkaline phosphatase activity and upregulated progesterone receptor messenger RNA (*43*).

Miscellaneous activity

Intragastric administration of three doses of an essential oil of the strobiles, 30 mg/animal, given over 2 days, stimulated the activity of glutathione-*S*-transferase in the liver and intestine of mice (*44*). Six flavonoid compounds isolated from the strobiles, 0.1–100.0 µmol/l, inhibited the growth of human breast cancer (MCF-7), colon cancer (HT-29) and ovarian cancer (A-2780) cells in vitro (*45*). Flavonoid compounds isolated from the strobiles, namely xanthohumol, isoxanthohumol and 8-prenylnaringenin, 10.0 µmol/l, inhibited the 7-ethoxyresorufin-*O*-deethylase activity of the CYP1A1 and CYP1A2 isozymes of cytochrome P450 (*46*).

Toxicology

The median lethal dose (LD_{50}) of orally administered ethanol extracts of the strobiles or lupulones in mice was found to be 500.0–3500.0 mg/kg bw (*29*). The oral LD_{50} in rats was 2700.0 mg/kg bw (*29*). The oral LD_{50} for lupulone was 525.0 mg/kg bw in mice and 1800.0 mg/kg bw in rats (*3*). The intraperitoneal LD_{50} of an ethanol extract of the strobiles in mice was 175.0 mg/kg bw (*17*).

Clinical pharmacology

In a small study without controls, oral administration of 250.0 mg of a lipophilic concentrate of the strobiles daily for 5 days to 15 healthy volunteers had no sleep-inducing effects (*47*).

Adverse reactions

Strobilus Lupuli may cause drowsiness (*31*).

Contraindications

Strobilus Lupuli is contraindicated in cases of known allergy to the plant material.

Warnings

No information available.

Precautions

Drug interactions

While no drug interactions have been reported, flavonoid constituents of Strobilus Lupuli have been shown to inhibit the activity of cytochrome P450, and concurrent administration of the strobiles with prescription drugs metabolized by these enzymes may adversely influence the pharmacokinetics of these drugs.

Carcinogenesis, mutagenesis, impairment of fertility

Subcutaneous administration of 20.0–50.0 mg/kg bw of purified fractions of the strobiles twice daily for 3 days to female rats pretreated by subcutaneous injection with 25 IU of pregnant mare's serum gonadotrophin did not induce any changes in uterine weight, but ovarian weight decreased significantly ($P < 0.05$) (*48*).

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; teratogenic or non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried strobiles and dried extracts for infusions and decoctions, dry extracts, fluidextracts, and tinctures (*7, 16*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Cut or powdered strobiles or dry powder for infusion, decoctions and other preparations, single dose of 0.5 g; liquid and solid preparations for internal use, infusion or decoction, 0.5 g in 150 ml of water; fluidextract 1:1 (g/ml) 0.5 ml; tincture 1:5 (g/ml) 2.5 ml; native dry extract 6–8:1 (w/w) 0.06–0.08 g (*16*).

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Gummi Myrrha

Definition

Gummi Myrrha consists of the air-dried oleo-gum resin exudates from the stems and branches of *Commiphora molmol* Engler (Burseraceae) and other related *Commiphora* species (*1–4*), including *C. abyssinica* Engl., *C. erythraea* and *C. schimperi* Engl. (*5*), but excluding *C. mukul*.

Synonyms

For *Commiphora molmol* Engl.: *Balsamodendron myrrha* Nees, *Commiphora myrrha* Holm, *C. myrrha* (Nees) Engl. var. *molmol* Engl. (*2, 6*).

Selected vernacular names

Abyssinian myrrh, arbre à myrrhe, bal, barakande, bisabol myrrh, bol, bola, dashi 'biskiti, gandharsh, guban myrrh, habaq-hagar-ad, heerbol, heerabol myrrh, hirabol myrrh, Männliche myrrhe, mbebe, mbele, mo yao, morr, morrh, mur, murr, myrr, myrrh, Myrrhenbaum, myrrha, molmol, myrrhe des somalis, ogo myrrh, turari, Somali myrrh (*1, 2, 6–11*).

Geographical distribution

Various *Commiphora* species are indigenous to arid and tropical regions of Africa. *Commiphora molmol* is indigenous to Somalia and is cultivated in the Arabian Peninsula and North Africa and in Ethiopia, India, Kenya and United Republic of Tanzania (*1, 2, 9*).

Description

Commiphora species are shrubs or small trees, about 3 m high, with rounded tops, thick trunks, dark brown bark and large, sharply pointed thorns on the stem. Branches numerous, irregular or rough, stunted and spiny. Leaves unequal, ternate, alternate. Flowers small, dioecious, yellow-red fascicled, polygamous, arranged in terminal panicles. Calyx tubular, teeth usually four, valvate petals usually found inserted on the edge of the disk; stamens 8–10 on disk alternately long and short filaments, dialated below. Fruits are oval-lanceolate drupes, about 0.3 cm

long. When stems are damaged or incised, oleo-gum resins exude from the schizogenous resin ducts (*1, 2, 7, 10*).

Plant material of interest: dried oleo-gum resin

General appearance

Rounded or irregular tears or lumps of agglutinated tears of variable sizes; brownish-yellow to reddish-brown or almost black. The surface is mostly covered with a greyish or yellowish powder; the internal surface is yellowish or reddish-brown, sometimes marked with white spots or lines; brittle; fracture, waxy, granular, conchoidal and yields thin translucent fragments (*1, 3, 7, 10*).

Organoleptic properties

Odour: characteristic, aromatic, balsamic; taste: aromatic, bitter, acrid (*1–3, 7, 10*).

Microscopic characteristics

Not applicable.

Powdered plant material

Not applicable.

General identity tests

Macroscopic (*1, 7, 10*) and microscopic (*10*) examinations; microchemical and spectroscopic tests (*1, 3, 7, 12*), and thin-layer chromatography (*2–4, 13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Total ash

Not more than 10.0% (*1*). Not more than 7.0 % (*4*).

Acid-insoluble ash

Not more than 5.0% (*1*).

Water-soluble extractive

Not less than 48% (*2*).

Alcohol-insoluble residue

Not more than 70.0% (*1, 4*).

Moisture
Not more than 15.0% (*4*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia* (*15*), and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*14*).

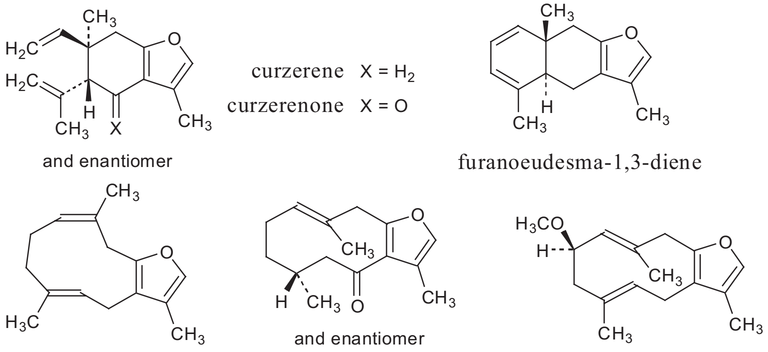
Other purity tests
Chemical and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays
Not less than 6% essential oil (*3*). Qualitative and quantitative high-performance liquid chromatography for furanosesquiterpenes (*17*).

Major chemical constituents
The oleo-gum resin obtained from *C. molmol* contains: resins (25–40%), essential oil (3–8%) and a water-soluble gum (30–60%) (*1, 18*). The gum is composed of 20% proteins and 65% carbohydrates made up of galactose, 4-O-methylglucuronic acid and arabinose. The major constituents of the essential oil are furanosesquiterpenes (*10*), and the monoterpenes α-, β- and γ–bisabolene. Representative structures are presented below.

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and well established documents
Topical treatment of mild inflammations of the oral and pharyngeal mucosa (*3, 19, 20*). As a gargle or mouth rinse for the treatment of aphthous ulcers, pharyngitis, tonsillitis, common cold and gingivitis (*3, 21*).



furanoeudesma-1,3-diene

furanodiene 4,5-dihydrofuranodien-6-one 2-methoxyfuranodiene

Uses described in traditional medicine

As an emmenagogue, expectorant and antidote for poisons, and to inhibit blood coagulation. Treatment of menopausal symptoms, arthritic pain, diarrhoea, fatigue, headache, jaundice and indigestion, and applied topically for treatment of burns and haemorrhoids (*9, 11, 22, 23*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of an aqueous suspension of Gummi Myrrha, 10% in saline solution, 10.0 ml/kg body weight (bw) had analgesic effects in mice, as assessed by the hot-plate test (*24*). Intragastric administration of 50.0 mg/kg bw of a sesquiterpene, furanoeudesma-1,3-diene, isolated from the resin also had analgesic effects in mice as measured by the acetic acid writhing test (*24*). Intragastric administration of 400.0 mg/kg bw of a 100% ethanol extract of the resin reduced writhing induced by acetic acid in mice by 25% (*25*). Intragastric administration of 500.0 mg/kg bw of a petroleum ether extract or a 95% ethanol extract of the resin significantly ($P < 0.05$) suppressed yeast-induced pyrexia in mice (*26, 27*).

Anticoagulant activity

Intraperitoneal administration of 100.0 mg/kg bw of an ethyl acetate extract of the resin inhibited platelet aggregation in mice. However, an aqueous extract of the resin given by the same route was not active (*28*). Intraperitoneal administration of 100.0 mg/kg bw of an ethyl acetate extract of the resin, had antithrombotic activity in mice (*29*).

Antihyperglycaemic activity

Intragastric administration of 10.0 ml/kg bw of a hot aqueous extract of the resin per day for 7 days, reduced blood glucose levels in diabetic rats (*30*). Intragastric administration of 150–175.0 mg/kg bw of two furanosesquiterpenes isolated from the resin significantly ($P < 0.0036$–0.0009) reduced blood glucose levels in genetically altered obese diabetic mice, measured 27 hours after administration (*31*).

Anti-inflammatory activity

Intragastric administration of 400.0 mg/kg bw of an aqueous extract of the resin to rats significantly ($P < 0.05$) reduced carrageenan-induced footpad oedema by up to 59% (*32*). Intragastric administration of 400.0 mg/kg bw of a petroleum ether extract of the resin per day for 18 days to rats with Freund's adjuvant-induced arthritis significantly ($P < 0.05$) reduced the development of inflammation (*32*). Intragastric administration of 80.0 mg/kg bw of a petroleum ether extract of the resin inhibited carrageenan-induced footpad oedema in rats (*33*). Intraperitoneal administration of 200–400.0 mg/kg bw of a 100% ethanol extract of the resin reduced xylene-induced ear inflammation in mice by 50% (*25*). Intragastric administration of 500.0 mg/kg bw of a petroleum ether extract of the resin reduced carrageenan-induced footpad oedema and cotton pellet-induced granuloma in rats (*26*).

Cytoprotectant activity

Intragastric administration of 250.0 mg/kg bw of an aqueous suspension of the resin reduced the formation of ulcers induced by ethanol, sodium chloride and indometacin in rats by increasing the production of gastric mucus (*34*).

Toxicology

An ethanol extract of the resin was administered to rats by gastric lavage (1000.0 mg/kg bw), intramuscular injection (500.0 mg/kg bw) or intraperitoneal injection (250.0 mg/kg bw) daily for 2 weeks. Depression, huddling, jaundice, ruffled hair, hepatonephropathy, haemorrhagic myositis and patchy peritonitis at the injection site, and death were observed. Increases in serum alanine phosphatase, alanine transferase activities, bilirubin, cholesterol and creatinine concentrations, and decreases in total protein and albumin levels, macrocytic anaemia and leukopenia were also seen. When the doses were halved, the adverse effects were reduced (*35*).

The oral lethal dose of the essential oil is 1.65 g/kg bw in rats (*36*). However, no deaths were reported in mice after intragastric administration of 3.0 g/kg bw of a 95% ethanol extract of the resin (*27*).

Intragastric administration of 1.0–5.0 g/kg bw of the resin per day to Nubian goat kids caused grinding of teeth, salivation, soft faeces, inappetence, jaundice, dyspnoea, ataxia and recumbency. Death occurred between days 5 and 16. Enterohepatonephrotoxicity was accompanied by anaemia, leukopenia, increases in serum alanine phosphatase activity and concentrations of bilirubin, cholesterol, triglycerides and creatinine, and decreases in total protein and albumin. An oral dose of 0.25 g/kg bw per day was not toxic (*37*).

In acute (24-h) and chronic (90-day) oral toxicity studies in mice, the resin was administered at doses of 0.5 g/kg bw, 1.0 g/kg bw or 3.0 g/kg bw, and 100.0 mg/kg bw per day, respectively. No significant increase in mortality was observed in either study. In the chronic study, however, there was an increase in body weight and increases in the weight of the testes, caudae epididymides and seminal vesicles in treated animals as compared with untreated controls. Treated animals also showed an increase in red blood cells and haemoglobin levels. No spermatotoxic effects were observed in treated animals (*38*).

Clinical pharmacology
No information available.

Adverse reactions
Topical application of a diluted (8%) solution of an essential oil obtained from the resin was non-irritating, non-sensitizing and non-phototoxic when applied to human skin (*36*). Application of an unspecified extract of the resin to human skin caused contact dermatitis (*39–41*).

Contraindications
Gummi Myrrha is used in traditional systems of medicine as an emmenagogue, and its safety during pregnancy has not been established. Therefore, in accordance with standard medical practice, Gummi Myrrha should not be used during pregnancy (*42, 43*).

Warnings
Use of the undiluted tincture may give rise to a transient burning sensation and irritation of the palate (*3*).

Precautions

Drug interactions
Although no drug interactions have been reported, internal ingestion of Gummi Myrrha may interfere with existing antidiabetic therapy owing to

the ability of the resin to reduce blood glucose levels. Patients taking anticoagulant drugs or with a history of bleeding disorders should consult their health-care provider prior to using the resin.

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of the resin, 40.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *Salmonella typhimurium* strains TA98 and TA100 (*44*). Intraperitoneal administration of an aqueous extract of the resin at doses 10–40 times the normal therapeutic dose did not have mutagenic effects (*44*). A hot aqueous extract of the resin, 40.0 mg/plate, inhibited aflatoxin B1-induced mutagenesis in *S. typhimurium* strains TA98 and TA100 (*45*). The genotoxic, cytotoxic and antitumour properties of the resin were investigated in normal mice and mice bearing Ehrlich ascites carcinoma cells. The genotoxic and cytotoxic activity was evaluated on the basis of the frequency of micronuclei and the ratio of polychromatic to normochromatic cells in the bone marrow of normal mice. Intragastric administration of 125.0–500.0 mg/kg bw of the resin did not have clastogenic effects, but was cytotoxic in normal mice. In the mice bearing tumours, the resin had antitumour activity, and was reported to be as effective as the antitumour agent cyclophosphamide (*46*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to the lack of data concerning the safety and efficacy of Gummi Myrrha, it should not be used by nursing mothers without consulting a health-care practitioner.

Paediatric use

Owing to the lack of data concerning the safety and efficacy of Gummi Myrrha, it should not be administered to children without consulting a health-care practitioner.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms

Powdered resin, capsules, myrrh tincture, and other galenical preparations for topical use (*20*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Myrrh tincture (1:5 g/ml, 90% ethanol), undiluted tincture applied to the affected area two or three times per day; mouth rinse or gargle, 5–10 drops of the tincture in a glass of water (*20*); mouthwash or gargle solution, 30–60 drops of the tincture in a glass of warm water (*19*); paint, undiluted tincture applied to the affected areas on the gums or the mucous membranes of the mouth with a brush or cotton swab, two or three times per day (*19*); dental powder, 10% powdered oleo-gum resin (*20*).

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Herba Passiflorae

Definition

Herba Passiflorae consists of the dried aerial parts of *Passiflora incarnata* L. (Passifloraceae) (*1–3*).

Synonyms

Granadilla incarnata Medik., *Passiflora kerii* Spreng. (*4*).

Selected vernacular names

Apricot vine, flor de la pasión, Fleischfarbene Passionsblume, fiore della passione, fleur de la passion, grenadille, maracujá, may apple, may flower, may-pop, pasionaria, passiflora, passiflora roja, passiflore, passion vine, rose-coloured passion flower, water lemon, white passion flower, wild passion flower (*2, 4–6*).

Geographical distribution

Indigenous to North America (*5, 7, 8*).

Description

A perennial, creeping herb, climbing by means of axillary tendrils. Leaves alternate, palmately three to five serrate lobes. Flowers large, solitary, with long peduncles, whitish, with a triple purple and pink crown. Fruits are ovate berries containing numerous ovoid, flattened seeds covered with a yellowish or brownish aril (*7*).

Plant material of interest: dried aerial parts

General appearance

Stems lignified, green, greyish-green or brownish, usually less than 5 mm in diameter; rounded, longitudinally striated and often hollow. Leaves alternate with furrowed, often twisted petioles, possessing two extra-floral nectaries at the apex; lamina 6–15 cm long, broad, green to brownish green, palmate with three to five lanceolate lobes covered with fine hairs

on the lower surface; margin serrate. Tendrils borne in leaf axils, smooth, round and terminating in cylindrical spirals. Flowers 5–9 cm in diameter with peduncles up to 8 cm long, arising in leaf axils; five, white, elongated petals; calyx of five thick sepals, upper surface green and with a horn-like extension; involucre of three pointed bracts with papillose margins; five large stamens, joined at the base and fused to the androgynophor; ovary greyish-green, superior; style hairy with three elongated stigmatic branches. Fruits 4–5 cm long, oval, flattened and greenish-brown containing numerous seeds 4–6 mm long, 3–4 mm wide and 2 mm thick, with a brownish-yellow, pitted surface (*2*).

Organoleptic properties
No distinctive odour; taste: bitter (*2*).

Microscopic characteristics
Transverse section of older stem shows epidermis of isodiametric cells with strongly thickened, convex external walls; some cells containing crystals of calcium oxalate, others developing uniseriate trichomes two to four cells long, terminating in a rounded point and frequently hooked; hypodermis consisting of a layer of tangentially elongated cells, outer cortex with groups of collenchyma, containing cells with brown, tanniferous contents; pericycle with isolated yellow fibres and partially lignified walls; inner cortex of parenchymatous cells containing cluster crystals of calcium oxalate; xylem consisting of groups of vessels up to 300 µm in diameter with pitted, lignified tracheids; pith of lignified parenchyma containing numerous starch grains 3–8 µm in diameter, simple or as aggregates. Leaf upper and lower epidermis shows sinuous anticlinal cell walls; numerous anomocytic stomata in the lower epidermis, which also has numerous uniseriate covering trichomes of one to three cells, terminal cells comparatively long, pointed and curved; groups of brown tannin cells occur in the marginal teeth and in the mesophyll; cluster crystals of calcium oxalate 10–20 µm in diameter isolated in the mesophyll or arranged in files associated with the veins. Sepal upper epidermis has large, irregular, polygonal cells with some thickened walls, striated cuticle, rare stomata and numerous small crystals of calcium oxalate; lower epidermis comprises two layers, the outer layer consisting of polygonal cells with numerous stomata and small crystals of calcium oxalate, the inner layer of smaller polygonal cells. Epidermal cells of the petals papillose, especially in the filiform appendices. Pollen grains 65–75 µm in diameter, with a cross-ridged surface and three acuminate germinal pores. Pericarp composed of large cells with few stomata and groups of calcium oxalate crystals; endocarp of thickened, sclerous cells (*2*).

Powdered plant material
Light green and characterized by fragments of leaf epidermis with sinuous cell walls and anomocytic stomata; numerous cluster crystals of calcium oxalate isolated or aligned along the veins; many isolated or grouped fibres from the stems associated with pitted vessels and tracheids; uniseriate trichomes with one to three thin-walled cells, straight or slightly curved, ending in a point or sometimes a hook. If flowers are present, papillose epidermis of the petals and appendages and pollen grains with a reticulate exine. If mature fruits are present, scattered brown tannin cells and brownish-yellow, pitted fragments of the testa (*3*).

General identity tests
Macroscopic and microscopic examinations (*2, 3*), and thin-layer chromatography for the presence of flavonoids (*2, 3, 9*).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Chemical
Contains not more than 0.01% harman alkaloids (*11*).

Foreign organic matter
Not more than 2% (*3*).

Total ash
Not more than 13% (*3*).

Acid-insoluble ash
Not more than 3.0% (*2*).

Water-soluble extractive
Not less than 15% (*2*).

Loss on drying
Not more than 10% (*3*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European pharmacopoeia*

(*12*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*13*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

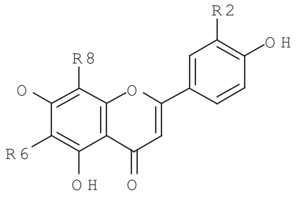
Other purity tests
Sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 1.5% of total flavonoids, expressed as vitexin, determined by spectrophotometry (*3*). A high-performance liquid chromatography method for flavonoids is also available (*14*).

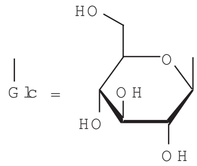
Major chemical constituents
The major constituents are flavonoids (up to 2.5%) with the principal compounds being the *C*-glycosyl of apigenin (R2 = H) and luteolin (R2 = OH), including mono-*C*-glucosyl derivatives isovitexin (up to 0.32%), iso-orientin and their 2''-β-D-glycosides, and di-*C*-glycosyl derivatives schaftoside (up to 0.25%), isoschaftoside (up to 0.15%) and swertisin (*1, 15, 16*). Also found are di-*C*-glucosyl derivatives vicenin-2 and lucenin-2 and small amounts of mono-*C*-glucosyl derivatives orientin and vitexin (*1*). Other chemical constituents include maltol (3-hydroxy-2-methyl-γ-pyrone) (0.05%), chrysin and a cyanogenic glycoside, gynocardin. Traces of the indole (β-carboline) alkaloids (e.g. harman, harmol, harmine) have been reported in the source plants; however, these alkaloids are undetectable in most commercial materials (*4–6, 8, 16*). The structures of the alkaloid harman and characteristic flavonoids are presented below.

Medicinal uses

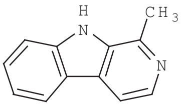
Uses supported by clinical data
None.

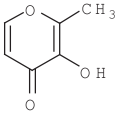


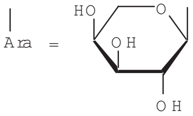
	R2	R6	R8
orientin	OH	H	Glc
iso-orientin	OH	Glc	H
lucenin-2	OH	Glc	Glc
schaftoside	H	Glc	Ara
isoschaftoside	H	Ara	Glc
vicenin-2	H	Glc	Glc
vitexin	H	H	Glc
isovitexin	H	Glc	H



β-D-glucopyranosyl

harman 

maltol 



α-L-arabinopyranosyl

Uses described in pharmacopoeias and well established documents

Internally as a mild sedative for nervous restlessness, insomnia and anxiety. Treatment of gastrointestinal disorders of nervous origin (*1, 5, 11*).

Uses described in traditional medicine

As an anodyne, antispasmodic and mild stimulant (*1, 6*). Treatment of dysmenorrhoea, neuralgia and nervous tachycardia (*1*).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 5.0 g/kg body weight (bw) of a 60% ethanol extract of Herba Passiflorae per day for 3 weeks to rats did not reduce the pain response as measured in the tail-flick test using radiant heat, and no reductions in body temperature were observed (*17*). Intragastric administration of a 30% ethanol extract of the aerial parts reduced phenylbenzoquinone-induced writhing in mice, median effective dose 1.9 ml/kg bw (*18*).

Anti-inflammatory activity

Intragastric administration of 75.0–500.0 mg/kg bw of an ethanol extract of the aerial parts to rats reduced carrageenan-induced inflammation in the hind-paw model 60 minutes after administration (*19*). Intragastric administration of 500.0 mg/kg bw of the same extract to rats significantly reduced (16–20%; $P < 0.05–0.001$) the weight of granulomas induced by the implantation of cotton pellets (*19*).

Total leukocyte migration into the rat pleural cavity was reduced by approximately 40% in rats with induced pleurisy following intragastric administration of 500.0 mg/kg bw of an ethanol extract of the aerial parts. This effect was due to the suppression of polymorphonuclear and mononuclear leukocyte migration, and the effect was similar to that of 250.0 mg/kg bw of acetylsalicylic acid (*19*).

Antimicrobial activity
A 50% ethanol extract of up to 500.0 mg/ml of the aerial parts did not inhibit the growth of the following fungi: *Aspergillus fumigatus, Botrytis cinerea, Fusarium oxysporum, Penicillium digitatum, Rhizopus nigricans* and *Candida albicans* (*20*). A methanol extract of the aerial parts inhibited the growth of *Helicobacter pylori*, minimum inhibitory concentration 50.0 µg/ml (*21*).

Cardiovascular effects
In vitro perfusion of guinea-pig heart with a 30% ethanol extract of the aerial parts, 0.001%, increased the force of contraction of the heart muscle. Intravenous administration of 0.05 ml/kg bw of the extract had no effect on blood pressure in guinea-pigs or rats (*18*).

Central nervous system depressant activity
Intraperitoneal injection of 25.0 mg/kg bw of an aqueous extract of the aerial parts to mice reduced spontaneous locomotor activity and coordination. However, intraperitoneal administration of the same dose of a fluidextract to mice did not reduce motor activity (*22*). Intraperitoneal or intragastric administration of 60.0–250.0 mg/kg bw of a 30% ethanol or 40% ethanol extract to mice reduced spontaneous locomotor activity. Intragastric administration of 60.0 mg/kg bw of the 40% ethanol extract also potentiated pentobarbital-induced sleeping time, and intraperitoneal administration of 50 mg/kg bw significantly ($P < 0.05$) delayed the onset of pentylenetetrazole-induced seizures (*23*).

The effects of an aqueous or 30% ethanol extract of the aerial parts were assessed in mice using the unconditioned conflict test, the light/dark box choice procedure and the staircase test. The extracts were administered at doses of 100.0 mg/kg bw, 200.0 mg/kg bw, 400.0 mg/kg bw or 800.0 mg/kg bw, while control animals received normal saline. The aqueous extract reduced motor activity in the staircase and free exploratory tests, as measured by the number of rears, steps climbed or locomotor crossings following administration of the 400.0 mg/kg and 800.0 mg/kg doses. The aqueous extract also potentiated pentobarbital-induction of sleep. The 30% ethanol extract was not active in these tests, but appeared

to increase activity of the animals, having an anxiolytic effect at the 400.0 mg/kg dose (*24*).

Intraperitoneal administration of 160.0–250.0 mg/kg bw of an aqueous extract of the aerial parts to mice delayed pentylenetetrazole-induced convulsions, increased pentobarbital-induced sleeping time and reduced spontaneous motor activity (*25*).

Intragastric administration of a 30% ethanol extract of the aerial parts, corresponding to 5.0 g/kg bw, per day for 3 weeks to rats had no effect on body weight, rectal temperature, tail-flick or motor coordination. However, in a one-armed radial maze, the treated animals demonstrated a reduction in motor activity. No changes were observed in electroencephalographic parameters in the treated animals (*17*).

Intragastric administration of 800.0 mg/kg bw of a dried 30% ethanol extract of the aerial parts (containing 2.6% flavonoids) to mice did not affect locomotor activity, but did prolong hexobarbital-induced sleeping time (*26*).

Chrysin displayed high affinity for the benzodiazepine receptors in vitro, and reduced locomotor activity in mice following intraperitoneal administration of 30.0 mg/kg bw (*27, 28*). At the same dose, chrysin also increased pentobarbital-induced hypnosis (*28*).

Uterine stimulant effects

A fluidextract of the aerial parts, 1.0 mol/l, stimulated strong contractions in guinea-pig and rabbit uterus (not pregnant) in vitro (*22*). However, a fluidextract, 1.0–2.0 mol/l, did not stimulate contractions in the isolated uterus from pregnant guinea-pigs (*29*).

Toxicology

The oral median lethal dose of a 30% ethanol extract of the aerial parts in mice was 37.0 ml/kg bw (*18*). Toxicity in mice of an aqueous extract was observed only after intraperitoneal administration of 900.0 mg/kg bw (*25*). No acute toxicity was observed in mice given extracts of the aerial parts at doses of 500.0 mg/kg bw or 900.0 mg/kg bw (*25, 30*).

Clinical pharmacology

No clinical data available for mono-preparations of Herba Passiflorae.

Adverse reactions

A single case of hypersensitivity with cutaneous vasculitis and urticaria following ingestion of tablets containing an extract of Herba Passiflorae was reported (*31*). In one case, use of the aerial parts was associated with IgE-mediated occupational asthma and rhinitis (*32*). A single case of se-

vere nausea, vomiting, drowsiness, prolonged QT segment and episodes of non-sustained ventricular tachycardia was reported in a female subject after self-administration of a therapeutic dose of the aerial parts (*33*). However, the clinical significance of this reaction has not been evaluated.

Contraindications

Herba Passiflorae has been shown to stimulate uterine contractions in animal models (*22*). Its use is therefore contraindicated during pregnancy.

Warnings

May cause drowsiness. The ability to drive a car or operate machinery may be impaired.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

A fluidextract of Herba Passiflorae was not genotoxic at concentrations up to 1.3 mg/ml in *Aspergillus nidulans*, as assessed in a plate incorporation assay that permitted the detection of somatic segregation as a result of mitotic crossing-over, chromosome mal-segregation or clastogenic effects. No significant increase in the frequency of segregant sectors per colony were observed at any tested dose (*34*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to the lack of data concerning its safety and efficacy, Herba Passiflorae should not be used by nursing mothers without consulting a health-care practitioner.

Paediatric use

Owing to the lack of data concerning its safety and efficacy, Herba Passiflora should not be administered to children without consulting a health-care practitioner.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; or teratogenic effects in pregnancy.

Dosage forms

Powdered dried aerial parts, capsules, extracts, fluidextract and tinctures (*5*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Daily dose, adults: as a sedative: 0.5–2.0 g of aerial parts three to four times; 2.5 g of aerial parts as an infusion three to four times; 1.0–4.0 ml tincture (1:8) three to four times; other equivalent preparations accordingly (*2, 11*).

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Testa Plantaginis

Definition

Testa Plantaginis consists of the epidermis and collapsed adjacent layers removed from the seeds of *Plantago ovata* Forsk. (Plantaginaceae) (*1, 2*).

Synonyms

Plantago brunnea Morris, *P. decumbens* Forsk., *P. fastigiata* Morris, *P. gooddingii* Nelson et Kennedy, *P. insularis* Eastw., *P. ispaghula* Roxb. ex Flem., *P. lanata* Willd. ex Spreng., *P. leiocephala* Wallr., *P. microcephala* Poir., *P. minima* Cunn., *P. trichophylla* Nab., *P. villosa* Moench. (*3*).

Selected vernacular names

Ashwagolam, aspaghol, aspagol, bazarqutuna, blond psyllium, Blondes Psyllium, Ch'-Ch'ientzu, esfarzeh, esopgol, esparzeh, fisyllium, ghoda, grappicol, Indian plantago, Indische Psyllium, isabakolu, isabgol, isabgul, isabgul gola, isapagala-vittulu, ishppukol-virai, ispaghula, isphagol, vithai, issufgul, jiru, kabbéche, lokmet an naâja, obako, psyllium, plantain, spogel seed plantain (*3–5*).

Geographical distribution

Indigenous to Asia and the Mediterranean countries. Cultivated extensively in India and Pakistan; adapts to western Europe and subtropical regions (*6–8*).

Description

An annual, acaulescent herb. Stem highly ramified bearing linear leaves, which are lanceolate, dentate and pubescent. Flowers white and grouped into cylindrical spikes; sepals characterized by a distinct midrib extending from the base to the summit; petal lobes oval with a mucronate summit. Seeds oval, clearly carinate, 2–3 mm long, light grey-pink, with a brown line running along their convex side (*6*).

Plant material of interest: dried seed coats (epidermis)

General appearance

Pinkish-beige fragments or flakes up to 2 mm long and 1 mm wide, some showing a light brown spot corresponding to the location of the embryo before it was removed from the seed (*2*).

Organoleptic properties

Odour: weak, characteristic; taste: mucilaginous (*9*).

Microscopic characteristics

Particles angular, edges straight or curved and sometimes rolled. Composed of polygonal prismatic cells with four to six straight or slightly curved walls; cells vary in size in different parts of the seed coat, from about 25–60 µm long at the summit of the seed to 25–100 µm for the remainder of the epidermis, except at the edges of the seed, where the cells are smaller, about 45–70 µm (*3*).

Powdered plant material

Pale to medium buff-coloured, having a slight pinkish tinge and a weak characteristic odour. Entire or broken epidermal cells, which appear polygonal to slightly rounded in surface view and are filled with mucilage. Occasional single and compound (two to four components) starch granules, the individual grains being spheroidal plano- to angular-convex 2–25 µm in diameter, embedded in the mucilage. Mucilage stains red with ruthenium red and lead acetate TS. Also present, some elongated and rectangular cells from the lower part of epidermis, and radially swollen epidermal cells (*2*).

General identity tests

Macroscopic and microscopic examinations (*2*) and thin-layer chromatography for the presence of arabinose, xylose and galactose (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Complies with the test for foreign matter determined on 5.0 g of material (*2*).

Total ash
Not more than 4% (*2*).

Loss on drying
Not more than 12% (*2*).

Swelling index
Not less than 40 (*2*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, sulfated ash, acid-insoluble ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
To be established in accordance with national requirements. *Plantago* products can be assayed for their fibre content by the Association of Official Analytical Chemists method (*13*).

Major chemical constituents
The major constituent is a mucilaginous hydrocolloid (20–30%), which is a soluble polysaccharide fraction composed primarily of an arabinoxylan (up to 85%). The polymer backbone is a xylan with 1→ 3 and 1→ 4 linkages with no apparent regularity in their distribution. The monosaccharides in this main chain are substituted on C-2 or C-3 by L-arabinose, D-xylose, and α-D-galacturonyl-(1→2)-L-rhamnose. Fixed oil (5–10%) is another major constituent (*5, 9, 14–16*).

Medicinal uses

Uses supported by clinical data

A bulk-forming laxative used therapeutically for restoring and maintaining bowel regularity (*15, 17–26*). Treatment of chronic constipation, temporary constipation due to illness or pregnancy, irritable bowel syndrome and constipation related to duodenal ulcer or diverticulitis (*18, 27*). Also indicated for stool softening in the case of haemorrhoids, or after anorectal surgery (*18, 20*). As a dietary supplement in the management of hypercholesterolaemia, to reduce the risk of coronary heart disease (*28*), and reduce the increase in blood sugar levels after eating (*24*).

Uses described in pharmacopoeias and well established documents

Short-term use for the symptomatic treatment of diarrhoea of various etiologies (*29–31*).

Uses described in traditional medicine

As an expectorant, antitussive and diuretic. Treatment of rheumatism, gout, glandular swelling and bronchitis (*5, 8*).

Pharmacology

Experimental pharmacology

Antidiarrhoeal activity

Intragastric administration of 0.4 g of Testa Plantaginis per day inhibited *Escherichia coli*-induced diarrhoea in pigs (*32*). Intragastric administration of the seed coats to calves, 18.89 g/l of oral rehydration solution, did not reduce the number or frequency of stools (*33*).

Antihypercholesterolaemic activity

Administration of the seed coats in the diet, 10%, to African green monkeys fed a high-cholesterol diet for 3.5 years significantly ($P < 0.05$) reduced plasma cholesterol levels by 39% and inhibited the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase in the liver and intestine (*34*). A further study in these animals also showed that this administration of the seed coats reduced plasma cholesterol concentrations by decreasing the synthesis of low-density lipoproteins (LDL) (*35*). Administration of the seed coats in the diet, 7.5%, to hamsters reduced cholesterol concentrations and increased sterol loss in the liver. The mechanism of action appears to involve a reduction of LDL cholesterol production and an increase in receptor-mediated LDL clearance (*36*). Administration of the seed coats, 7.5 g/100 g body weight (bw) daily to guinea-pigs fed a high-cholesterol diet significantly ($P < 0.0001$) reduced plas-

ma cholesterol levels by 39% as compared with controls (*37*). Alterations in hepatic cholesterol metabolism were observed in guinea-pigs after the administration of the seed coats (dose not specified). Treated animals fed a high fat and sucrose diet showed reductions in plasma LDL cholesterol, triacylglycerol, apolipoprotein B and hepatic cholesteryl ester concentrations, and a 45% increase in the number of hepatic apolipoprotein A/E receptors (*38*).

Administration of Testa Plantaginis in the diet, 5.0%, to rats reduced serum cholesterol concentrations (*39*). Administration of the seed coats in the diet, 10.0%, reduced total serum cholesterol concentrations and increased high-density lipoprotein (HDL) cholesterol in rats fed a high-cholesterol diet (*40*). Administration of the seed coats in the diet, 5.0%, to rats significantly ($P < 0.0001$) lowered an increase in serum cholesterol concentrations induced by feeding the animals trans-fatty acids (corn-oil margarine) (*41*).

Antihyperglycaemic activity

Administration of the seed coats in the diet, 2.5%, for 18 weeks to mice with genetically-induced diabetes reduced blood glucose levels and increased blood insulin concentrations (*42*).

Effects on bile acids

Administration of the seed coats in the diet, 5.0%, for 5 weeks to rats increased bile acid synthesis and lowered the hydrophobicity of the bile acid pool (*43*). Administration of the seed coat in the diet, 5.0%, to dogs fed a lithogenic diet for 6 weeks reduced the incidence of cholesterol gallstones by reducing the biliary cholesterol saturation index (*44*). Administration of the seed coats in the diet, 4.0–6.0%, for 5 weeks to hamsters fed a lithogenic diet increased faecal bile acid excretion by 400%, and reduced the concentration of taurine-conjugated bile acids in those receiving the highest dose. In addition, the treatment normalized the lithogenic index and prevented cholesterol gallstone formation as compared with controls (*45*). Administration of the seed coats in the diet, 8.0%, for 5 weeks to hamsters increased daily faecal neutral sterol excretion by 90% owing to higher faecal output. Daily faecal bile acid excretion and total faecal bile acid concentrations were also increased (*46*).

Gastrointestinal effects

Administration of the seed coats in the diet, 10.0–20.0%, for 4 weeks to rats resulted in increased levels of gastric, intestinal and colonic mucin, and increased faecal weight compared with control animals (*47*). In vitro,

a 70% methanol extract of the seed coats, 6.0 mg/ml, stimulated contractions of isolated guinea-pig ileum (*48*).

Clinical pharmacology

Antidiarrhoeal activity

In patients with acute and chronic diarrhoea, 10 g of Testa Plantaginis per day for 7 days increased the viscosity of the intestinal contents, owing to the binding of fluid by the seed coats, thereby decreasing the frequency of defecation (*29, 30*).

In a placebo-controlled trial, 10 female patients with diarrhoea-predominant irritable bowel syndrome were treated with 3.4 g of the seed coats three times per day for 4 weeks after an initial 4-week baseline placebo period. The treatment significantly improved patient global satisfaction with bowel function ($P < 0.02$), and urge to defecate ($P < 0.01$) compared with placebo. Treatment also reduced movement frequency and doubled stool viscosity (*31*).

Eight subjects participated in a randomized, placebo-controlled crossover study on the moderation of lactulose-induced diarrhoea in irritable bowel syndrome. Gastric emptying and small bowel and colonic transit were measured following consumption of 20 ml of lactulose three times per day with or without 3.5 g of Testa Plantaginis three times per day. The seed coats significantly delayed gastric emptying by 50% ($P < 0.05$); small bowel transit was unchanged, and progression through the colon was delayed. It was concluded that the seed coats probably delayed gastric emptying by increasing meal viscosity, and reduced the acceleration of colon transit by delaying the production of gaseous fermentation products (*49*).

Antihypercholesterolaemic activity

Numerous clinical investigations with the seed coats have demonstrated a reduction in serum cholesterol levels in patients with mild to moderate hypercholesterolaemia (*23, 26*). A meta-analysis assessed the hypolipidaemic effects and safety of the seed coats when used as an adjunct to a low-fat diet in men and women with hypercholesterolaemia. Eight clinical trials met the criteria for the meta-analysis and included a total of 384 and 272 subjects receiving the seed coats or cellulose placebo, respectively. All of the trials evaluated the hypocholesterolaemic effects of 10.2 g of the seed coats daily together with a low-fat diet for ≥ 8 weeks. Consumption of seed coats significantly lowered serum total cholesterol by 4% ($P < 0.0001$), LDL cholesterol by 7% ($P < 0.0001$), and the ratio of apolipoprotein B to apolipoprotein A-I by 6% ($P < 0.05$) compared with pla-

cebo. No effects on serum HDL or triacylglycerol concentrations were observed (*26*).

Another meta-analysis assessed the efficacy of the consumption of a cereal product enriched with the seed coats in reducing blood total, LDL and HDL cholesterol levels in 404 adults with mild to moderate hypercholesterolaemia, who were also consuming a low-fat diet. Studies were considered to be eligible for inclusion in the meta-analysis if they were randomized controlled trials, and included a control group that ate cereal containing at least 3.0 g of soluble fibre daily. Eight published and four unpublished studies, conducted in four countries, met the criteria. The results of the meta-analysis demonstrated that subjects who consumed cereals containing the seed coats had lower total and LDL cholesterol concentrations, with differences of 5% and 9%, respectively, than subjects who ate a control cereal; HDL cholesterol concentrations were unaffected. The analysis indicates that consumption of cereals enriched with the seed coats as part of a low fat diet improves the blood lipid profile in hypercholesterolaemic adults to a greater extent than the low-fat diet alone (*23*).

A multicentre clinical investigation assessed the long-term effectiveness of Testa Plantaginis fibre as an adjunct to diet in the treatment of primary hypercholesterolaemia. Subjects were required to follow an American Heart Association Step I diet for 8 weeks (dietary adaptation phase). Eligible subjects with serum LDL-cholesterol concentrations of 3.36–4.91 mmol/l were then randomly assigned to receive 5.1 g of the seed coats or a cellulose placebo twice per day for 26 weeks in conjunction with diet therapy. The results demonstrated that serum total and LDL cholesterol concentrations were 4.7% and 6.7% lower, respectively, in the treatment group than in the placebo group after 24–26 weeks ($P < 0.001$) (*25*). A multicentre, double-blind, placebo-controlled, randomized trial assessed the cholesterol-level-lowering effect of the seed coats with dietary advice compared with placebo and dietary advice in 340 patients with mild-to-moderate hypercholesterolaemia. An initial 8-week diet-only period was followed by a 2-week treatment period. Treatment with 7.0 g or 10.5 g of the seed coats per day was continued for a further 12 weeks in some patients. Levels of total, LDL and HDL cholesterol, triglycerides and apolipoproteins A1 and B were measured. Treatment with the seed coats at both doses produced significantly greater reductions in LDL cholesterol levels than did placebo ($P = 0.009$ and $P < 0.001$). The seed coats plus modification of diet reduced LDL cholesterol levels by 10.6–13.2% and total cholesterol levels by 7.7–8.9% during the 6-month period (*50*).

A randomized controlled clinical trial assessed the effects of the seed coats as an adjunct to a traditional diet for diabetes in the treatment of 34 subjects with type 2 diabetes and mild-to-moderate hypercholesterolaemia. After a 2-week dietary stabilization phase, subjects were randomly assigned to receive 5.1 g of the seed coats or cellulose placebo twice per day for 8 weeks. The group treated with the seed coats showed significant improvements in glucose and lipid values as compared with the placebo group. Serum total and LDL-cholesterol concentrations were 8.9% ($P < 0.05$) and 13.0% ($P = 0.07$) lower, respectively, than in the placebo group. All-day and post-lunch postprandial glucose concentrations were 11.0% ($P < 0.05$) and 19.2% ($P < 0.01$) lower in the treated group (*24*).

In a clinical trial, the diet of six normal and five ileostomy subjects was supplemented with 10.0 g of the seed coats per day for 3 weeks, while six normal and four ileostomy subjects received 10.0 g of *Plantago ovata* seeds per day. Faecal and ileostomy output, sterol excretion, serum cholesterol and triglycerides were measured before and after supplementation. The seed coats had no effect on cholesterol or triglyceride concentrations in either normal or ileostomy subjects. Total and HDL cholesterol concentrations were reduced on average by 6.4% and 9.3%, respectively, in the normal group after seed supplementation. No effect on faecal bile acid excretion in the normal subjects was found in either group. Ileostomy bile acids were increased (on average 25%) after seed supplementation, whereas no effect on cholesterol concentrations was found. These results suggest that the seeds might be more effective than the seed coats in reducing serum cholesterol, that this cholesterol-lowering effect is not mediated by increased faecal bile acid losses, and that increased ileal losses of bile acids might be compensated for by enhanced reabsorption in the colon (*51*).

In a double-blind, placebo-controlled study involving 26 men, supplementation of the diet with 3.4 g of the seed coats three times per day for 8 weeks produced a decrease in serum cholesterol (-14.8%) and LDL cholesterol (-20.2%) (*52*). In a similar study, in which the seed coats were added to a low-fat diet, improvements in cholesterol parameters were observed after 8 weeks of therapy (*53*). The reduction in serum cholesterol may be due to increased excretion of bile acids in the faeces, which in turn stimulates synthesis of new bile acids from cholesterol (*22, 54*).

In a clinical study to assess the effect of the seed coats on faecal bile acid weights and concentrations, 16 healthy adults consumed 7.0 g of the seed coats per day for the middle 8 weeks of a 12-week period. Stool samples were collected and analysed for faecal bile acid content, and their form and dry weight were determined. Administration of the seed coats

significantly ($P < 0.01$) lowered faecal lithocholic and isolithocholic acids and the weighted ratio of lithocholic acids to deoxycholic acid. The change in the faecal bile acid profile indicates a reduction in the hydrophobicity of the bile acids in the enterohepatic circulation (*55*).

Laxative activity

Administration of the seed coats, solubilized in water, increases the volume of the faeces by absorbing fluids in the gastrointestinal tract, thereby stimulating peristalsis (*56*). The seed coats also reduce intraluminal pressure, increase colon transit time, and increase the frequency of defecation (*18, 20, 57*). Soluble fibres, such as those contained in the seed coats, are rapidly metabolized by colonic bacteria to volatile fatty acids, which are then absorbed by the colon, and increase the production of colonic mucin.

The therapeutic efficacy of the seed coats is due to the swelling of the mucilaginous fibre when mixed with water, which gives bulk and lubrication (*22*). The seed coats increase stool weight and water content owing to the water-bound fibre residue, and an increased faecal bacterial mass (*18, 20*). Clinical studies have demonstrated that ingestion of 18.0 g of the seed coats increases faecal fresh and dry weights as compared with placebo (*15*).

The digestibility of the seed coats and their faecal bulking effect were studied in seven healthy volunteers who ingested a low-fibre diet plus either placebo or the seed coats, 18 g/day, during two 15-day periods. There were no differences between the groups in whole gut transit time and gas excretion in breath and flatus. Faecal wet and dry weights rose significantly ($P = 0.009$ and $P = 0.037$, respectively) in the treated subjects. Faecal short-chain fatty acid concentrations and the molar proportions of propionic and acetic acids also increased in the treated group (*15*).

Adverse reactions

Sudden increases in dietary fibre may cause temporary gas and bloating. These side-effects may be reduced by a gradual increase of fibre intake, starting at one dose per day and gradually increasing to three doses per day (*58*). Occasional flatulence and bloating can be reduced by decreasing the amount of the seed coats taken for a few days (*58*).

Allergic reactions to ingestion or inhalation of *Plantago* products have been reported, especially after previous occupational exposure to these products (*59–64*). These reactions range from urticarial rashes to anaphylactic reactions (rare) (*60, 65*). One rare case of fatal bronchospasm has been reported in a Testa Plantaginis-sensitive patient with asthma (*62*).

Contraindications

Testa Plantaginis should not be used by patients with faecal impaction, undiagnosed abdominal symptoms, abdominal pain, nausea or vomiting unless advised by their health-care provider. Testa Plantaginis is also contraindicated following any sudden change in bowel habits that persists for more than 2 weeks, in rectal bleeding or failure to defecate following use of a laxative, and in patients with constrictions of the gastrointestinal tract, potential or existing intestinal blockage, megacolon, diabetes mellitus that is difficult to regulate, or known hypersensitivity to the seed coats (*14*, *22*).

Warnings

To minimize the potential for allergic reaction, health professionals who frequently dispense powdered products prepared from Testa Plantaginis should avoid inhaling airborne dust while handling these products. To prevent generating airborne dust, the product should be spooned from the packet directly into a container and then the liquid should be added (*58*).

Testa Plantaginis products should always be taken with sufficient amounts of liquid, e.g. 5.0 g of the seed coats with 150 ml of liquid. Failure to do so may result in swelling of the seed coats and blockage of the oesophagus, which may cause choking. Intestinal obstruction may occur if an adequate fluid intake is not maintained. The seed coats should not be used by those with difficulty in swallowing or throat problems. Anyone experiencing chest pain, vomiting or difficulty in swallowing or breathing after taking Testa Plantaginis should seek immediate medical attention. Treatment of the elderly and the debilitated requires medical supervision.

Testa Plantaginis should be taken at least 2 h before or after other medications to prevent delayed absorption of other drugs (*66*). If bleeding, or no response and abdominal pain occur 48 h after ingesting the seed coats, treatment should be discontinued and medical advice sought (*58*).

Precautions

General

Testa Plantaginis should be taken with adequate volumes of fluid. Products should never be taken orally in dried powder form owing to possibility of causing bowel or oesophageal obstruction. In patients confined to bed or undertaking little physical exercise, a medical examination may be necessary prior to treatment with the seed coats.

Drug interactions
Bulking agents may diminish the absorption of some minerals (calcium, magnesium, copper and zinc), vitamins (B_{12}), cardiac glycosides and coumarin derivatives (*3, 52, 67–68*). However, more recent studies suggest that since seed coats do not contain phytates, they will not bind to vitamins and minerals and are therefore no cause for concern (*69–71*). The co-administration of the seed coats with lithium salts may reduce plasma concentrations of the latter and inhibit their absorption from the gastrointestinal tract (*72*). The seed coats may also decrease the rate and extent of carbamazepine absorption, and induce subclinical levels of the drug. Ingestion of lithium salts or carbamazepine and the seed coats should therefore be separated by as long an interval as possible (*73*). Ingestion of the seed coats 2 hours before or after the administration of other drugs is suggested (*66*). Individual monitoring of the plasma levels of these drugs, especially in patients also taking products containing Testa Plantaginis is also recommended. Insulin-dependent diabetics may require less insulin (*14*).

Other precautions
No information available on precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms
Dried seed coats available commercially as chewable tablets, granules, wafers and powder. Store in a well closed container, in a cool dry place, protected from light (*2, 19*).

Posology
No information available.

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Radix Rehmanniae

Definition

Radix Rehmanniae consists of the dried roots and rhizomes of *Rehmannia glutinosa* Libosch. or *Rehmannia glutinosa* Libosch. var. *purpurea* Makino (Scrophulariaceae) (*1–4*).[1]

Synonyms

Digitalis glutinosa Gaertn., *Gerardia glutinosa* Bunge, *Rehmannia chinensis* Libosch., *R. sinensis* (Buc'hoz) Libosch. ex Fisch. et C.A. Mey. (*5*).

Selected vernacular names

Akayajio, di-huang, cû sinh dja, dihuang, dihuáng, dja hoâng, figwort, ji-whang, rehmannia, sheng dihuang, sheng-ti-pien, shu di, sin dja, ti huang (*4–7*).

Geographical distribution

Indigenous to China. Cultivated in China, Japan and Republic of Korea (*6, 8*).

Description

A perennial herb 10–40 cm high, with a thick, orange tuberous root, about 3–6 cm in diameter. Basal leaves fasciculate, obovate or long elliptic, 3–10 cm long, 1.5–2.0 cm wide; apex obtuse; tapering to a short petiole, coarsely dentate, pubescent, the underside often reddish. Flowers are solitary, borne in leaf axils; calyx five-lobed, upper lobes longest; corolla obliquely funnel form, slightly swollen on lower side, about 4 cm long, dull purple-brown and creamy yellow, densely glandular-pubescent, two-lipped; upper lobes shorter than the three lower lobes; tube with two ridges extending inside from sinuses of lower lip; four stamens borne near

[1] In the *Pharmacopoeia of the People's Republic of China* (*4*), fresh plant material is also permitted. In *The Japanese Pharmacopoeia* (*2*), steam-treated root material is also permitted.

base of corolla, anthers not coherent, disc ring-like, poorly developed; ovary superior, stigma two-lobed. Fruits are capsules (*6, 8*).

Plant material of interest: dried roots and rhizomes

General appearance

Fusiform root, 5–12 cm long, 1–6 cm in diameter, often broken or markedly deformed in shape. Externally, yellow-brown to blackish brown, with deep, longitudinal wrinkles and constrictions. Texture soft and tenacious, not easily broken. In transverse section yellow-brown to blackish brown, and cortex darker than xylem in colour. Pith hardly observable (*1, 2, 4*).

Organoleptic properties

Odour: characteristic; taste: slightly sweet, followed by a slight bitterness (*1, 2, 4*).

Microscopic characteristics

Transverse sections of the root show 7–15 layers of cork cells. Cortex parenchyma cells loosely arranged. Outer region of cortex composed of scattered secretory cells containing orange-yellow oil droplets. Stone cells occasionally found. Phloem relatively broad. Cambium is in a ring. Xylem rays broad, vessels sparse and arranged radially (*1, 2, 4*).

Powdered plant material

Dark brown. Cork cells brownish, subrectangular in lateral view, regularly arranged. Parenchyma cells subrounded, containing subrounded nuclei. Secretory cells similar to ordinary parenchyma cells in shape, containing orange or orange-red oil droplets. Border pitted and reticulated vessels up to about 92 µm in diameter (*3, 4*).

General identity tests

Macroscopic and microscopic examinations (*1–4*), and thin-layer chromatography (*3, 4*). A high-performance liquid chromatography method for catalpol, the major iridoid monoterpene, is available (*9*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Total ash
Not more than 6% (*1, 2, 4*).

Acid-insoluble ash
Not more than 2.5% (*1, 2*).

Water-soluble extractive
Not less than 65% (*3, 4*).

Pesticide residues
The recommended maximum limit for aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*), and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

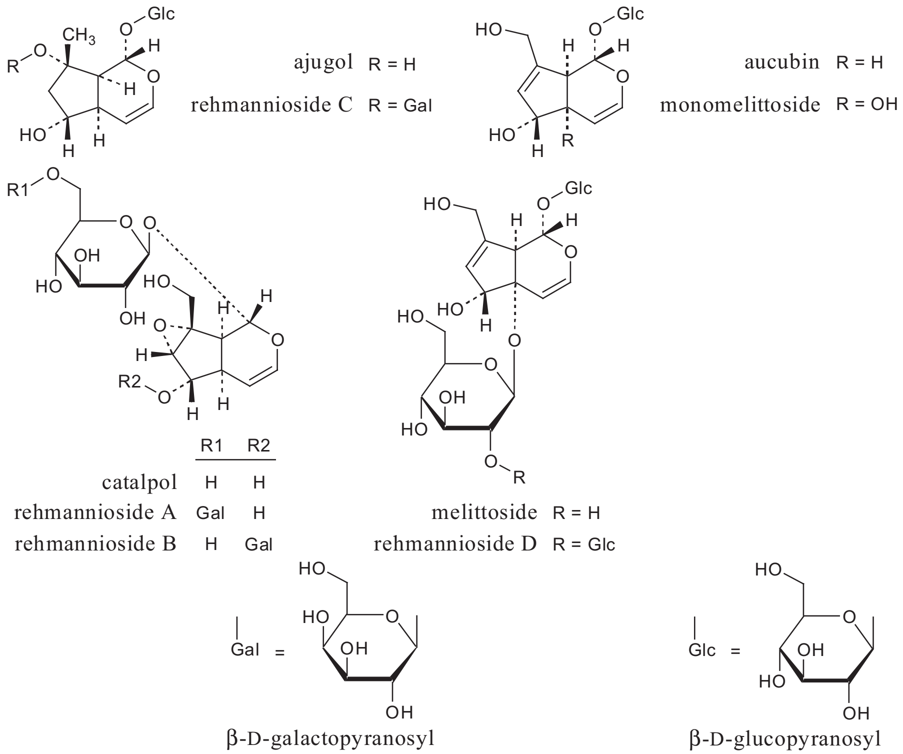
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter, sulfated ash, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

Chemical assays
To be established in accordance with national requirements.

Major chemical constituents
The major constituents are iridoid monoterpenes (2.6–4.8%) (*13*) including catalpol, ajugol, aucubin, rehmanniosides A–D, monomelittoside, melittoside, verbascoside, jionosides A1, A2, B1, B2, C, D and E (*5, 7, 14, 15*). In addition, immunomodulating polysaccharides have also been reported (*16–18*). Representative structures of the iridoid monoterpenes are presented below.



Medicinal uses

Uses supported by clinical data

None. Although published case reports indicate that Radix Rehmanniae is used for the treatment of rheumatoid arthritis and hypertension (*19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Internally for the symptomatic treatment of fevers, diabetes, hypertension, skin eruptions and maculation, sore throat, hypermenorrhoea and polymenorrhoea (*4*, *20*). As a tonic to stimulate the immune system (*21*).

Uses described in traditional medicine

As an antispasmodic, diuretic and emmenagogue. Treatment of burns, diarrhoea, dysentery, metrorrhagia and impotence (*7*, *20*, *22*, *23*).

Pharmacology

Experimental pharmacology

Antibacterial activity

A hot aqueous extract of Radix Rehmanniae (concentration not specified) did not inhibit the growth of *Staphylococcus aureus* or *Escherichia coli* in vitro (*24*).

Antidiarrhoeal activity

Intragastric administration of 2.0 g/kg body weight (bw) of an aqueous extract of the roots had no effects on serotonin-induced diarrhoea in mice (*25*).

Antihepatotoxic activity

A decoction of the roots, 25.0 µl/ml, inhibited hepatitis antigen expression in cultured hepatocytes infected with hepatitis B virus (*26*). An 80% methanol extract of the roots, 1.0 mg/ml, significantly inhibited ($P < 0.05$) the release of lactate dehydrogenase, glutamate-oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) induced by carbon tetrachloride treatments in rat hepatocytes (*27*).

Intraperitoneal administration of 500.0 mg/kg bw of a methanol extract of roots to rats inhibited the increase in blood alkaline phosphatase, GOT and GPT activities caused by hepatotoxicity induced by α-naphthyl-isothiocyanate or carbon tetrachloride (*28, 29*).

Antihyperglycaemic activity

Intragastric administration of an aqueous or methanol extract of the roots, 200.0 mg/kg bw or 111.5 mg/kg bw, to rats decreased streptozocin-induced hyperglycaemia (*30*). However, no such effects were observed in diabetic rats treated orally with 1.6–2.0 g/kg bw of a hot aqueous extract or a decoction of the roots daily for 8 days. These data suggest that the chemical constituents responsible for the activity may be heat sensitive (*31–33*).

Intraperitoneal administration of 100.0 mg/kg bw of a polysaccharide-enriched extract of the roots to mice decreased streptozocin-induced hyperglycaemia, reduced the activities of glucose-6-phosphatase and phosphofructokinase, stimulated the activities of glucose-6-phosphate dehydrogenase and hexokinase, and stimulated insulin release from the pancreas (*34*).

Anti-inflammatory activity

Intragastric administration of 200.0 mg/kg bw of a 50% ethanol extract of the roots to rats did not inhibit carrageenan-induced footpad oedema or adjuvant-induced arthritis (*35*).

Antitumour activity

After 24 h of treatment with polysaccharides isolated from the roots, 0.1 mg/ml, p53 gene expression in Lewis lung cancer cells increased almost four-fold (*36*). Intraperitoneal administration of 20.0 mg/kg bw or 40.0 mg/kg bw of polysaccharides isolated from the roots to mice increased the expression of the proto-oncogene c-fos by ~50% and decreased the expression of c-myc by ~ 30% compared with administration of saline (*37*). Intraperitoneal administration of 20.0–40.0 mg/kg bw of a polysaccharide isolated from the roots daily for 8 days after the second day of tumour transplantation inhibited the growth of solid tumours S180, Lewis B16, and H22 in mice. Oral treatment was only effective against S180. Treatment also enhanced the proliferation of splenic T lymphocytes and blocked the inhibition of natural killer cell activity caused by tumour cell growth (*16*).

Antiulcer activity

Intragastric administration of 6.0 g/kg bw of an aqueous extract of the roots to rats reduced absolute ethanol-induced gastric mucosal damage by 74.7%. The protective effects of the extract were reduced when the animals were pretreated with a decoction of chilli fruits (40–80%), suggesting that they were mediated by capsaicin-sensitive neurons in the gastric mucosa (*38*).

Central nervous system depressant effects

Intragastric administration of 2.5 g/kg bw of an aqueous extract of the roots prolonged pentobarbital-induced sleeping time in mice with stress- or yohimbine-induced sleep deprivation (*39*).

Enzyme-inhibiting effects

A petroleum ether extract of the roots inhibited the activity of aldose reductase, median inhibitory concentration (MIC) 8.5 µg/ml (*40*). An aqueous extract of the roots (concentration not specified) inhibited the activity of angiotensin II (*41*). A decoction of the roots inhibited the activity of a sodium/potassium adenosine triphosphatase isolated from horse kidney, MIC 5.76 mg/ml. A 95% ethanol extract of the roots was not active in this assay (*42*).

Haematological effects

Intragastric administration of 10.0–20.0 mg/kg bw of an oligosaccharide fraction isolated from the roots daily for 8 days to senescence-accelerated mice enhanced DNA synthesis in bone marrow cells, increased the number of granulocyte/macrophage progenitors, and increased early-

and late-differentiated erythrocyte progenitors (*43*). Intragastric administration of (10.0–20.0 mg/kg bw of an oligosaccharide fraction isolated from the roots to senescence-accelerated mice enhanced the proliferation of hematopoietic stem cells, and increased the number of colony-forming-unit granulocytes/macrophages, colony-forming- and burst-forming-unit erythroid cells, and the concentration of peripheral leukocytes (*44*). Intragastric administration of a decoction of the roots (dose not specified) to mice inhibited blood clotting induced by acetylsalicylic acid (*45*). A 50% ethanol extract of the roots increased erythrocyte deformability and erythrocyte ATP concentrations, and inhibited polybrene-induced erythrocyte aggregation and the activity of the fibrinolytic system (*46*). Intragastric administration of 200.0 mg/kg bw of a 50% extract of the roots to rats inhibited the reduction of fibrinolytic activity and erythrocyte deformability, decrease in erythrocyte counts, and increase in connective tissue in the thoracic artery in arthritis induced by chronic inflammatory adjuvant (*35*). Intragastric administration of a 50% ethanol extract of the roots (dose not specified) to rats increased blood flow in the dorsal skin, abdominal vein and spleen tissue (*47*).

Immunological effects

Intraperitoneal administration of 10.0 mg/kg bw or 20.0 mg/kg bw of a polysaccharide extract isolated from the roots to mice bearing sarcoma 180 tumours increased cytotoxic T-lymphocyte activity on day 9 after administration, but did not significantly change interleukin-2 concentrations (*48*). In another study, administration of the same polysaccharide at the same dose to mice with the same tumour prevented the suppression of cytotoxic T lymphocyte activity and interleukin 2 secretion caused by excessive tumour growth (*49*). Intraperitoneal administration of 0.1 mg/kg bw of an aqueous extract of the roots to mice 1 hour prior to treatment with compound 48/80 inhibited compound 48/80-induced fatal shock by 53.3% and reduced plasma histamine release (*21*). In rat peritoneal mast cells, the same extract, 1.0 mg/ml, significantly ($P < 0.05$) inhibited anti-dinitrophenol IgE-induced histamine release and tumour necrosis factor-α production (*21*).

Intragastric administration of 100.0 mg/kg bw of jionoside B and verbascoside isolated from the roots to mice produced a 36% and 18% suppression of haemolytic plaque-forming cells in the spleen, respectively, compared with a 52.5% suppression following the administration of cyclophosphamide (*50*).

Platelet aggregation inhibition
Aqueous, hexane and methanol extracts of the roots, 1.0%, inhibited platelet aggregation induced by adenosine diphosphate, arachidonic acid and collagen in isolated rat platelets (*51*).

Toxicology
Intragastric administration of 60.0 g/kg bw of a decoction of the roots per day for 3 days to mice produced no adverse effects or death of the animals (*19*). Intragastric administration of 18.0 g/kg bw of a decoction of the roots per day for 45 days to rats produced no change in body weight or liver enzymes (*19*). Intragastric administration of 600.0 mg/kg bw of a 90% methanol extract of the roots per day for 4 days to mice had no toxic effects and did not induce weight loss (*52*). Intragastric administration of 400.0 mg/kg bw of a 90% methanol extract of the roots per day for 4 days to mice inhibited DNA synthesis in the bone marrow (*52*). The median oral lethal dose of a 70% methanol extract of the roots in mice was >2.0 g/kg (*53*).

Clinical pharmacology
Treatment of 23 cases of arthritis with a decoction of the roots (dose not specified) improved symptoms in most patients. Patients reported a decrease in joint pain, a reduction in swelling and improvements in joint movement. In addition, a normalization of the erythrocyte sedimentation rate was observed (*19*).

A decoction of the roots, corresponding to 30.0–50.0 g of roots, administered daily for 2 weeks to 62 patients with hypertension reduced blood pressure, serum cholesterol and triglycerides, and improved cerebral blood flow and the electrocardiogram (no further details available) (*19*).

Adverse reactions
Diarrhoea, abdominal pain, oedema, fatigue, vertigo and heart palpitations have been reported. However, these adverse effects were transient and disappeared within several days (*19*, *54*).

Contraindications
Radix Rehmanniae is contraindicated in chronic liver or gastrointestinal diseases and in patients with diarrhoea (*3*). Owing to its potential anti-implantation effects (*55*), the use of Radix Rehmanniae during pregnancy is also contraindicated.

Warnings
No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of Radix Rehmanniae, 40.0–50.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay using *Salmonella typhimurium* strains TA98, and TA100 (*56, 57*). However, intraperitoneal administration of 4.0 mg/kg bw of the aqueous extract to mice, equal to 10–40 times the amount used in humans, was mutagenic (*57*). Intraperitoneal administration of a hot aqueous extract of the roots (dose not specified) to mice did not enhance cyclophosphamide-induced chromosomal damage (*58*). Subcutaneous administration of a hot aqueous extract of the roots (dose not specified) inhibited embryonic implantation in treated female mice (*55*). No effects were observed after in vitro treatment of human sperm with an aqueous extract of the roots, 100.0 mg/ml (*59*).

Pregnancy: teratogenic effects

No teratogenic or abortifacient effects were observed in rats following intragastric administration of 500.0 mg/kg bw of a 70% methanol extract of the roots starting on the 13th day of pregnancy (*53*).

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to a lack of data on the safety and efficacy of Radix Rehmanniae, its use by nursing mothers is not recommended without supervision by a health-care provider.

Paediatric use

Owing to a lack of data on the safety and efficacy of Radix Rehmanniae, its use in children is not recommended without supervision by a health-care provider.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms

Dried roots and rhizomes for infusions and decoctions. Store in a well-closed container in a cool, dry place, protected from light (*4*).

Posology

(Unless otherwise indicated)
Daily dose: 9–15 g of dried roots and rhizomes as an infusion or decoction (*4*).

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Fructus Schisandrae

Definition

Fructus Schisandrae consists of the dried ripe fruits of *Schisandra chinensis* (Turcz.) Baill. (Schisandraceae) (*1–3*).[1]

Synonyms

Idesia polycarpa Morr. et de Vos, *Kadsura chinensis* Turcz., *Maximowiczia amurensis* Rupr., *M. chinensis* Rupr., *M. sinensis* Rupr., *Maximowitschia japonica* A. Gray, *Polycarpa maximowiczii* Morr. et de Vos, *Schisandra chinensis* var. *typica* Nakai, *Schizandra japonica* Sieb. et Zucc., *Sphaerostemma japonicum* A. Gray (*4*).

Selected vernacular names

Bac ngu vi tu, bei wuweizi, Chinesischer Limonenbaum, Chinese magnolia vine, Chinese mock-barberry, chosen-gomishi, lemonwood, limonnik kitajskij, matsbouza, m mei gee, ngu mei gee, northern magnoliavine, o-mee-ja, o-mi-d'ja, o-mi-ja, omicha, ornija, pen ts'ao, schisandra, dheng-mai-yin, wu-wei-zi, wu-weitzu (*4–8*).

Geographical distribution

Indigenous to Russia (Primorsk and Khabarovsk regions, the Kuril islands, southern Sakhalin) north-eastern China, Japan and the Korean peninsula. Cultivated in China and Republic of Korea (*7, 9*).

Description

A deciduous woody climbing vine, up to 8 m long. Leaves alternate, petiolate, ovate or oblong-obovoid, 5–11 cm long, 2–7 cm wide, apex acute or acuminate; base cuneate or broadly cuneate, membranous. Flowers uni-

[1] The *Pharmacopoeia of the People's Republic of China (3)* also recognizes the fruits of *Schisandra sphenanthera* Rehd. et Wils.

sexual, dioecious, solitary or clustered axillary, yellowish-white to pinkish; male flower stalked, with five stamens, filaments united into a short column; female flower has numerous carpels. Fruits, 5–8 mm in diameter, arranged into a long spike with globular, deep-red berries. Seeds, one to two per berry, reniform, shiny, smooth, yellowish brown, 4.5 mm long, 3.5 mm in diameter (*5, 7, 9, 10*).

Plant material of interest: dried ripe fruits

General appearance

Irregularly spheroidal or compressed-spheroidal, 5–8 mm in diameter. Externally dark red to blackish-red or covered with “white powder”, wrinkled, oily, with soft pulp. Seeds, one to two, reniform, externally brownish-yellow to dark red-brown, lustrous, with distinct raphe on the dorsal side; testa thin and fragile (*1, 3*).

Organoleptic properties

Odour of pulp: slight; odour of seed: aromatic on crushing; taste of pulp: sour; taste of seed: pungent and slightly bitter (*1, 3*).

Microscopic characteristics

Pericarp with one layer of square or rectangular epidermal cells, walls relatively thickened, covered with cuticle, oil cells scattered. Mesocarp with 10 or more layers of parenchymatous cells containing starch grains, scattered with small collateral vascular bundles. Endocarp with one layer of parenchymatous cells. Outermost layer of testa consists of radially elongated stone cells, thick walled, with fine and close pits and pit canals; then several lower layers of stone cells, subrounded, triangular or polygonal with larger pits, and a few layers of parenchymatous cells and raphe, with vascular bundles. Endosperm cells contain yellowish-brown coloured oil droplets and aleurone grains (*3*).

Powdered plant material

Dark purple in colour. Stone cells of epidermis of testa polygonal or elongated-polygonal in surface view, 18–50 µm in diameter, wall thickened with very fine and close pit canals, lumina containing dark brown contents. Stone cells of the inner layer of the testa polygonal, subrounded or irregular, up to 83 µm in diameter, walls slightly thickened, with relatively large pits. Epidermal cells of the pericarp polygonal in surface view, anticlinal walls slightly beaded, with cuticle striations, scattered with oil cells. Mesocarp cells shrivelled, with dark brown contents and starch granules (*3*).

General identity tests

Macroscopic and microscopic examinations (*1–3*), and thin-layer chromatography for the presence of deoxyschizandrin (schisandrin A) (*2, 3, 7*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*11*).

Foreign organic matter

Not more than 1.0% (*1, 3*).

Total ash

Not more than 5.0% (*1, 2*).

Acid-insoluble ash

Not more than 1.0% (*2*).

Water-soluble extractive

Not less than 35% (*2*).

Alcohol-soluble extractive

Not less than 40% (*2*).

Moisture

Not more than 8.0% (*2*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European pharmacopoeia* (*12*) and the WHO guidelines on quality control methods for medicinal plants (*11*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*11*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*11*) for the analysis of radioactive isotopes.

Other purity tests

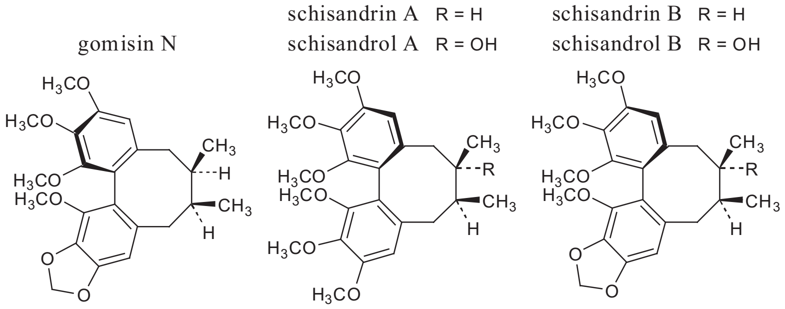
Chemical tests to be determined in accordance with national requirements.

Chemical assays

Contains not less than 0.4% schizandrin (schisandrin, schisandrol A, wuweizichun A) determined by high-performance liquid chromatography (*3*). Additional high-performance liquid chromatography and high-performance liquid chromatography–mass spectrometry methods are available (*14, 15*).

Major chemical constituents

The major constituents are lignans of biological interest with the dibenzo[*a,c*]cyclooctadiene skeleton. Among the approximately 30 lignans are schizandrin (schisandrin, schisandrol A, wuweizichun A, 0.2–0.7%), gomisin A (schisandrol B, wuweizichun B, wuweizi alcohol B, 0.1–3.0%), deoxyschizandrin (deoxyschisandrin, schisandrin A, wuweizisu A, 0.1–9.0%), (±)-γ-schizandrin (schisandrin B, γ-schisandrin B, wuweizisu B, 0.1–5.0%), and gomisin N (pseudo-γ-schisandrin B, 0.1–0.5%) (*7, 8*). The structures of schizandrin, deoxyschizandrin, gomisin N, gomisin A and (±)-γ-schizandrin are presented below:



Medicinal uses

Uses supported by clinical data

None. Although some clinical evidence supports the use of Fructus Schisandrae for the treatment of psychosis, gastritis, hepatitis and fatigue (*16, 17*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Treatment of chronic cough and asthma, diabetes, urinary tract disorders. As a general tonic for treating fatigue associated with illness (*3, 7, 9, 16*).

Uses described in traditional medicine

As an astringent, antitussive, antidiarrhoeal, expectorant and sedative (*8*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

External application of gomisin A (schisandrol B), 0.6 mg/ear, inhibited inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in mice. External application of gomisin J and schisandrin C also inhibited the inflammation induced by TPA in mice. The median effective dose (ED_{50}) of these compounds ranged between 1.4 µmol and 4.4 µmol, with gomisin A having the strongest anti-inflammatory effect (*18*).

Antihepatotoxic activities

In vivo studies have demonstrated that the fruits have liver-protectant effects. Intragastric administration of 80.0 mg/kg bw of a lignan-enriched extract of the fruits to rats prevented hepatotoxicity induced by carbon tetrachloride, prevented glutathione depletion and stimulated the activity of glutathione reductase (*19, 20*). In experimental models, the activity of serum glutamic pyruvic transaminase (SGPT) induced by the administration of carbon tetrachloride or paracetamol in mice, thioacetamide in rats, and ethinyl estradiol 3-cyclopentylether in rabbits was reduced by oral administration of 1.0–10.0 g/kg bw of a 95% ethanol extract of fruits (*21, 22*). A 95% ethanol extract of the fruits lowered elevated SGPT levels in mice treated with carbon tetrachloride or thioacetamide (*23*). Lignans, isolated from the fruits, have also been shown to have liver-protectant activities in vivo (*24, 25*). Intragastric administration of the lignans to mice, specifically 50.0 mg/kg bw of gomisin A, 50.0 mg/kg bw of gomisin B, 50.0–100.0 mg/kg bw of schisandrin A, 50–100.0 mg/kg bw of schisandrin B and 50.0–100.0 mg/kg bw of γ-schisandrin, decreased elevated SGPT levels in mice treated with carbon tetrachloride (*25*). Treatment with the lignans also prevented the elevation of SGPT levels and the morphological changes in the liver, such as inflammatory infiltration and liver cell necrosis, induced by carbon tetrachloride. Intragastric administration of 100 mg/kg bw of gomisin A, B or schisandrin also protected against thioacetamide-induced liver damage in mice (*23, 25*).

Oral pretreatment of rats with 50.0 mg/kg bw of gomisin A prevented the rise in SGPT and serum glutamic oxaloacetic transaminase (SGOT), as well as necrosis of hepatocytes induced by paracetamol (*26*). Intragastric administration of 30.0 mg/kg bw or 100.0 mg/kg bw of gomisin A per day for 4 days, increased liver weight in normal rats or animals with liver injury. Gomisin A suppressed the increase in serum transaminase activity and the appearance of histological changes, such as hepatocyte degeneration and necrosis, inflammatory cell infiltration and fatty depo-

sition induced by carbon tetrachloride, galactosamine or ethionine. Gomisin A also increased the activities of microsomal cytochrome B5, P450, NADPH cytochrome C reductase, aminophenazone-*N*-demethylase and 7-ethoxycoumarin *O*-deethylase, and decreased the activity of 3,4-benzopyrene hydroxylase (*27*).

Intragastric administration of 10.0–100.0 mg/kg bw of gomisin A per day for 4 days increased liver regeneration in rats after partial hepatectomy, increased the regeneration rate of the liver cells, and improved the serum retention rate of the foreign dye sulfobromophthalein. In addition, gomisin A enhanced the incorporation of radiolabelled phenylalanine into liver protein and decreased hexobarbital-induced sleeping time. Ultrastructural studies of liver tissue by electron microscopy showed an increase in rough and smooth endoplasmic reticulum in the groups receiving gomisin A. Gomisin A enhanced the proliferation of hepatocytes and the recovery of liver function after partial hepatectomy and increased hepatic blood flow. Liver enlargement induced by repeated administration of gomisin A may be due to the proliferation of endoplasmic reticulum (*27*). Intragastric administration of 10.0 mg/kg bw or 30.0 mg/kg bw of gomisin A per day for 3 or 6 weeks decreased fibrosis and accelerated liver regeneration and the recovery of liver function after partial hepatectomy in rats with chronic liver damage induced by carbon tetrachloride (*28*). Intragastric administration of 100.0 mg/kg bw of gomisin A per day for 14 days promoted hepatocyte growth after mitosis during regeneration of partially resected rat liver, and induced proliferation of non-parenchymal cells by increasing the c-*myc* product, a gene that precedes DNA replication in proliferating cells (*29*).

In vitro studies with cultured rat hepatocytes treated with an ethyl ether, ethyl acetate, methanol or water extract of the fruits, 0.1–1.0 mg/ml, reduced cytotoxicity induced by galactosamine and carbon tetrachloride (*30*). Gomisin A, 0.1 mg/ml, suppressed the biosynthesis of leukotrienes induced by calcium ionophore A2318 in rat peritoneal macrophages. This effect was partially associated with its antihepatotoxic effects (*31*).

Intragastric administration of 100.0–200.0 mg/kg bw of schisandrol A or schisandrin B reduced liver malondialdehyde formation induced by the administration of 50% ethanol to rats (*32*). Intragastric administration of 4.0–16.0 mg/kg bw of schisandrin B per day for 3 days increased the activities of hepatic glutathione *S*-transferase (GST) and glutathione reductase in mice treated with carbon tetrachloride (*33*). The mechanism by which schisandrin B exerts its hepatoprotectant effect appears to be through the enhancement of the hepatic glutathione antioxidant status in mice with carbon tetrachloride induced hepatotoxicity (*34, 35*). The ac-

tivities of glucose-6-phosphate dehydrogenase, selenium-glutathione peroxidase and γ-glutamylcysteine synthetase were reduced in a dose-dependent manner by schisandrin B (*33*). Pretreatment of mice with 1.0 mg/kg bw of schisandrin B per day for 3 days protected the animals against menadione-induced hepatic oxidative damage, and reduced the plasma level of alanine aminotransferase and the hepatic level of malondialdehyde as compared with menadione-intoxicated controls (*36*).

Intragastric administration of 12.0 mg/kg bw schisandrin B per day for 3 days to mice increased the hepatic mitochondrial glutathione concentration, whereas butylated hydroxytoluene decreased hepatic glutathione (*34*). Pretreatment with schisandrin B at the same dose sustained the hepatic mitochondrial glutathione level in carbon tetrachloride intoxicated mice and protected against carbon tetrachloride induced hepatotoxicity. Schisandrin B also increased the hepatic ascorbic acid (vitamin C) level in control animals, and sustained a high concentration of hepatic vitamins C and E in carbon tetrachloride intoxicated mice, which may partially explain its mechanism of action. Pretreatment of mice with intragastric administration of 1.2–12.0 mg/kg bw schisandrin B per day for 3 days had a dose-dependent protective effect on carbon tetrachloride induced lipid peroxidation and hepatocellular damage (*37*).

Administration of the powdered fruits in the diet, 5%, to mice induced a three-fold increase in activity of hepatic cytochrome P450. Total benzopyrene metabolism was increased 1.6-fold, and phenol II formation relative to total metabolites was significantly increased as compared with the control group. In addition, 7-ethoxycoumarin *O*-deethylase and aryl hydrocarbon hydroxylase activities were increased and the binding of aflatoxin to DNA was decreased (*38*).

Antioxidant activity

Inhibition of lipid peroxidation in rat liver microsomes was observed after treatment with schisandrol, schisandrin C and schisandrin B, 1.0 mmol/l, in vitro (*39*). Schisandrol and schisandrin B, 1.0 mmol/l, inhibited gossypol-induced superoxide anion generation in rat liver microsomes (*40*). Schisandrol, 1 mmol/l, scavenged oxygen radicals in human neutrophils induced by tetradecanoylphorbol acetate (*41*). Schisandrin B suppressed lipid peroxidation induced by carbon tetrachloride in hepatocytes in vitro (*42*). The release of GPT and lactate dehydrogenase was also reduced, thereby increasing hepatocyte viability and the integrity of the hepatocyte membrane (*39*). Schisandrin B, 10 mmol/l, inhibited NADPH oxidation in mouse liver microsomes incubated with carbon tetrachloride (*43*). Schisandrin B, 110.0 µmol/l, inhibited oxidation of erythrocyte membrane lipids induced by ferric chloride in vitro (*37*).

Antitumour activity

The effect of gomisin A on hepatocarcinogenesis induced by 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) in rats was assessed. Oral administration of 30 mg/kg bw of gomisin A per day for 5 weeks inhibited the appearance in the liver of foci for GST (placental form, GST-P), a marker enzyme of preneoplasm. Gomisin A also decreased the number of altered hepatic foci, such as the clear cell and basophilic cell type, in the early stages (*44*, *45*). Administration of gomisin A in the diet, 0.03%, for 10 weeks decreased the concentration of GST-P, and the number and size of GST-P positive foci in the liver after treatment with 3'-MeDAB (*46*). This indicates that gomisin A may inhibit 3'-MeDAB-induced hepatocarcinogenesis by enhancing the excretion of the carcinogen from the liver and reversing the normal cytokinesis (*47*).

Central nervous system effects

Intraperitoneal administration of 10.0 mg/kg bw of a 50% ethanol extract of the fruits to mice potentiated the sedative effects of barbiturates (*48*). However, intraperitoneal administration of 5.0 mg/kg bw of an ethanol and petroleum ether extract of the fruits decreased barbiturate-induced sleeping times (*49*). Intraperitoneal administration of 50.0 mg/kg bw of an unspecified extract of the fruits to mice 30 minutes prior to the injection of pentobarbital, ethanol, or exposure to ether significantly reduced the sleeping time of the treated group by 41.4%, 51.5% and 27%, respectively ($P < 0.001$ for all differences) (*50*). However, other researchers have demonstrated that the effects of the fruits on pentobarbital sleeping time depended upon the time of administration, and the type of extract or individual schisandrin derivatives administered. Schisandrin B or schisandrol B, 12.5 mg/kg bw, administered 1 hour prior to the injection of pentobarbital potentiated sleeping time. However, if the compounds were administered 24 hours prior to injection of pentobarbital, a decrease in sleeping time was observed. Administration of schisandrin C prolonged pentobarbital-induced sleeping time regardless of when it was administered (*24*).

Effects on drug metabolism

The activity of the fruits in restoring hepatic drug metabolism and phase I oxidative metabolism in livers damaged by carbon tetrachloride was investigated in vivo by assessing the pharmacokinetics of antipyrine (*51*). Intragastric administration of 160.0 mg/kg bw of a lignan-rich extract of the fruits to rats 30 minutes prior to administration of carbon tetrachloride and a single dose of antipyrine improved antipyrine elimination, decreased its clearance and reduced the half-life of the drug. In addition,

normalization of the levels of SGPT and SGOT and cytochrome P450 was observed (*51*).

Intragastric administration of 200.0 mg/kg bw of schizandrin B and schisanhenol per day for 3 days increased liver GST and microsomal cytochrome P450 levels in mice and rats. Both compounds reduced an increase in uterus weight in animals treated with estradiol, and decreased serum estradiol levels in mice. An enhancement in metabolism by liver microsomes, specifically the induction of drug-metabolizing phase I and phase II enzymes was also noted (*52*).

Ergogenic effects

The effects of the fruits on fatigue in and the endurance of horses has been assessed in a number of small studies. In one study, a dried 50% ethanol extract of the fruits or saline solution (48 g) was administered orally to thoroughbred horses prior to an 800-m race at maximum speed and to polo horses before a 12-minute gallop at a speed of 400 m/min. Treatment of the animals with the extract reduced serum lactic acid levels and increased plasma glucose levels after the test. Horses treated with the extract were also able to run faster and completed the 800-m race in 50.4 seconds compared with 52.2 seconds for the control animals ($P < 0.05$), indicating an increase in physical performance (*53*).

In a randomized double-blind, crossover study, 12.0 g of a dried 50% ethanol extract of the fruits, standardized to contain 1.2% schizandrins, was administered orally to 20 race horses 30 minutes prior to competition. Horses treated with the extract had significantly reduced heart rates for up to 20 minutes following the race ($P < 0.01$). The rate of respiration was also reduced immediately after the race, and was maintained for 15 minutes ($P < 0.05$). In addition, plasma glucose concentrations increased significantly ($P < 0.05$) and concentrations of lactic acid were significantly lower ($P < 0.01$) in the treated group than in the control group. Treated horses also completed the circuit in a shorter time than controls (117.5 seconds compared with 120.3 seconds) (*54*). A placebo-controlled study involving 24 sports horses with performance problems, as well as high levels of serum γ-glutamyltransferase (SGT), SGOT and creatinine phosphokinase, assessed the effects of the fruits on performance. Oral administration of 3.0 g of a dried 50% ethanol extract of the fruits per day to 12 horses significantly reduced SGT, SGOT and creatinine phosphokinase levels ($P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively), and improved performance after 7 and 14 days, as compared with 12 placebo controls (*55*).

Intragastric administration of 1.6 g/kg bw of a petroleum ether extract of the fruits to rats significantly ($P < 0.01$) reduced exercise-induced elevation of plasma creatine phosphokinase (*56*).

Toxicology

Intragastric administration of 0.6 g/kg bw or 1.3 g/kg bw of the fruits per day for 10 days to mice resulted in only mild toxic effects, such as decreased physical activity, piloerection, apathy and an increase in body weight (*57*). The intragastric and intraperitoneal median lethal doses (LD_{50}) of a petroleum ether extract of the fruits in mice were 10.5 g/kg bw and 4.4 g/kg bw, respectively. The symptoms of toxicity included depressed motor activity, short cataleptic periods and a lack of coordination of motor functions, which were followed by tonic seizures and marked mydriasis (*58*). In a 7-day study, no deaths occurred after oral administration of high doses of schisandrins A and C (2000.0 mg/kg bw), and schisandrol A (500.0 mg/kg bw); schisandrol B (250.0 mg/kg bw) and schisandrin B (250.0 mg/kg bw) showed relatively higher levels of toxicity (*24*).

The toxicity of an ethanol extract containing schisandrin B, and of the schisandrins A and C, 2000.0 mg/kg bw) and schisandrol A, 1000.0 mg/kg bw, was reported after intragastric administration to mice. Death of mice occurred within 7 days after administration of schisandrins A and C. Schisandrol B, 500 mg/kg bw, is reported to have a relatively higher toxicity after intragastric administration to mice. The LD_{50} of schisandrol B in mice is reported to be 878.0 mg/kg bw by the intragastric route and 855.0 mg/kg bw after subcutaneous administration. The intragastric LD_{50} values for petrol-ether extracts with schisandrin contents of 10%, 40% and 80% were 10.5 g/kg bw, 2.8 g/kg bw and 1.4 g/kg bw, respectively (*4*).

Clinical pharmacology

Studies on healthy subjects

Oral administration of 5–10.0 mg/kg bw of a 70% ethanol extract of the fruits, reduced fatigue and increased the accuracy of telegraphic transmission and reception by 22% (*59*). In another study, healthy male volunteers were given an oral preparation of the fruit (dose and form not specified), and were required to thread a needle at the same time as taking a message delivered through headphones. The results demonstrated that when compared to other undefined stimulants, the extract increased the accuracy and quality of work (*57*).

Other uncontrolled investigations have demonstrated that oral administration of the fruits increases physical performance in human subjects. A decrease in fatigue and acceleration of recovery after exercise were reported for athletes, such as long-distance runners, skiers and gymnasts, after consuming 1.5–6.0 g of the fruits daily over a 2-week period (*60*).

The effect of the fruits on physical stress was investigated in a controlled study involving 59 airline stewardesses (aged 22–29 years) during seven nonstop 9-hour flights. The study measured several stress parameters before and after the flights, with and without treatment with 0.5 g of an undefined extract of the fruits. Control subjects displayed a significant increase in heart rate ($P < 0.001$) and blood pressure ($P < 0.01$) during flights, while those taking the extract did not. The report further described the effect of oral administration of 2.0 g of an extract of the fruits to 58 untrained soldiers (aged 19–23 years) and 62 highly trained sportsmen (aged 19–30 years). Physical work capacity as measured by a step-ergometer, significantly increased 24 hours after treatment ($P < 0.05$), while that of the controls remained the same (*61*).

A double-blind, placebo-controlled clinical trial assessed the effects of a standardized extract of the fruits on the concentration of nitric oxide in human saliva, blood neutrophils, lymphocytes and monocytes, and working capacity, as a measure of adaptogenic potential in heavy exercise. The level of nitric oxide in the saliva of beginner athletes was found to increase after exercise while that in the saliva of well-trained athletes was high and did not increase further after exercise. Tablets containing an extract of the fruits, 91.1 mg standardized to 3.1 mg of schisandrin and γ-schisandrin, were administered twice daily for 8 days. There was a significant increase in the pre-exercise levels of nitric oxide in both beginners ($n = 17$) and athletes ($n = 46$) ($P < 0.05$); there were no changes in the other parameters (*62*).

A placebo-controlled clinical trial involving 134 healthy subjects assessed the effects of a single administration of the encapsulated fruits on night vision and acceleration of adaptation to darkness. Visual function was assessed 15–20 minutes prior to administration and 3 hours after. Administration of a single dose of 3.0 g of the fruits increased visual acuity under low illumination and extended the visual field margins for white and red colours by 8–25° (*16*). In a second study of 150 subjects, a single administration of 3 g of the fruits increased visual acuity in 90% of subjects. Administration of the drug decreased the time recognition of an object in darkness (from 32.3 seconds to 18.4 seconds), 4.5 hours after administration (*63*).

Clinical trials in patients

In an uncontrolled study, a tincture of the fruits was used for the treatment of stomach and duodenal ulcers in 140 patients with acute and chronic ulcers, who had been ill for 1–10 years. Patients were treated with 30–40 drops per day for 3–4 weeks. All subjects reported a reduction in symptoms within a few days, with ulcer healing reported in 96.5% of patients after 35 days of treatment. Recurrent episodes of peptic ulcer

disease were reported in only 9 of 90 patients followed over a period of 1–6 years (*64*).

A review of the Chinese literature mentioned reports of more than 5000 cases of hepatitis treated with preparations of the fruits, which had resulted in reductions of elevated liver enzymes. Elevated SGPT activities returned to normal in 75% of treated patients after 20 days of treatment. In subjects with elevated SGPT due to drug toxicity, SGPT levels reportedly returned to normal in 83 of 86 cases after 1–4 weeks of treatment. Enzyme levels reportedly decreased even without the discontinuation of the hepatotoxic drugs (*17*). It must be stressed that these are uncontrolled observational studies with questionable methodology. Further well designed, controlled clinical trials are needed to ascertain their validity.

In a controlled trial involving 189 patients with chronic viral hepatitis B and elevated SGPT levels, an ethanol extract of the fruits, containing 20 mg of lignans and corresponding to 1.5 g of the fruits, was administered orally to 107 of the patients daily, while the control group (n = 82) received liver extracts and vitamins (*65*). Normal SGPT levels were observed in 72 (68%) of patients receiving the extract after 4 weeks. In the control group, normal SGPT levels were observed in 36 (44%), with an average recovery time of 8 weeks. However, improvements in SGPT were only temporary, and levels rose again 6–12 weeks after treatment was discontinued. Relapse rates were highest (46–69%) in chronic persistent hepatitis, elderly patients, and in those receiving long courses of treatment with hepatotoxic drugs. Most patients responded to resumption of treatment with a return to their previously reduced SGPT levels (*17, 65*).

Adverse reactions

Minor adverse effects such as heartburn, acid indigestion, stomach pain, anorexia, allergic skin reactions and urticaria have been reported (*66*).

Contraindications

No information available.

Warnings

Symptoms of overdose include restlessness, insomnia or dyspnoea (*67*).

Precautions

Drug interactions

The fruits may have depressant effects on the central nervous system and should not therefore be used in conjunction with other CNS depressants,

such as sedatives or alcohol. They have been shown to stimulate the activity of hepatic cytochrome P450 (*68*). While no drug interactions have been reported, co-administration of prescription drugs metabolized through cytochrome P450, such as cyclosporin, warfarin, protease inhibitors, St John's wort, estrogen and progesterone combinations, should only be undertaken under the supervision of a health-care provider, owing to the inductive effects of the fruits on phase I and II drug-metabolizing enzymes (*51, 52*).

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous or methanol extract of the fruits was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, or in the *Bacillus subtilis* H-17 recombination assay at concentrations of up to 100.0 mg/ml (*69, 70*).

Pregnancy: non-teratogenic effects

In one uncontrolled investigation, 20–25 drops of a tincture (70% ethanol) of the fruits were administered to pregnant women three times per day for 3 days. Induction of labour was observed after the second dose followed by an increase in active labour 2–3 hours after the initial induction. The activity was most pronounced in women who had previously given birth. Shortened labour times were reported and no negative effects regarding blood pressure, elimination of the placenta, or postnatal health of mother and infant were observed (*7, 71*). In another investigation, an increase in the amplitude of uterine contractions (28 mm compared with 5 mm in controls) and uterine tension was observed after subcutaneous administration of 0.1 ml/kg bw of a tincture of the fruits to pregnant rabbits. The activity was observed 1.5 hours after administration and persisted for 4 hours (*71*).

A study conducted on women living in the Bryansk region of Ukraine, near the site of the Chernobyl nuclear reactor accident, assessed the effects of adaptogen administration on the health status of developing fetuses in pregnant women exposed to constant low-level radiation. The symptoms of placental insufficiency improved, fetal protein status was stabilized, obstetric complications were reduced, and the health status of the newborn infants was improved. No substantiating data were provided in this report, and no information regarding the preparations or dosages administered or the effect of the preparation on uterine contractions was given (*7, 72*).

Owing to a lack of further safety data regarding the effect of Fructus Schisandrae on neonatal development, its use during pregnancy is not recommended (*7*).

Nursing mothers

Owing to a lack of safety data, the use of Fructus Schisandrae during nursing is not recommended.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; teratogenic effects in pregnancy; or paediatric use.

Dosage forms

Dried fruits and tinctures, extracts and powders prepared from the fruits. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average daily dose: 1.5–6.0 g of the dried fruits (*3*).

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Radix Scutellariae

Definition
Radix Scutellariae consists of the dried roots of *Scutellaria baicalensis* Georgi (Lamiaceae) (*1–4*).

Synonyms
Scutellaria grandiflora Adams, *S. lanceolaria* Miq., *S. macrantha* Fisch. (*5*). Lamiaceae are also known as Labiatae.

Selected vernacular names
Baical skullcap, huang chin, huang lien, huang qin, huangqin, hwanggum, hwang-keum, Koganebana, skull cap, senohgon, whang-geum, whangegum, wogon (*3, 6, 7*).

Geographical distribution
Indigenous to the Korean peninsula and to China, Japan, Mongolia and Russian Federation (*6, 8, 9*).

Description
A spreading perennial herb up to 20–60 cm high. Stems erect, tetragonal, branching near base, glabrous or pubescent in the stem margins. Leaves opposite, simple, with short petioles 2 mm long; limb lanceolate, 1.5–4.0 cm long, 5 mm wide; tip obtuse, entire. Flowers blue to purple, in racemes. Calyx campanulate, bilabiate, the superior lip with a crest at the back; corolla tube long, much longer than the calyx, enlarged towards the top, swelling at the base; limb bilabiate; stamens four, didymous, fertile, ascending under the superior lip; anthers ciliate; ovary superior. Fruits are collections of small tuberculate nutlets, nearly globular, leathery (*6, 8*).

Plant material of interest: dried roots

General appearance
Conical, twisted or flattened root, 5–25 cm long, 0.5–3.0 cm in diameter. Externally yellow brown, with coarse and marked longitudinal wrinkles,

and with scattered scars of lateral root and remains of brown periderm; scars of stem or remains of stem at the crown; xylem rotted in old roots; hard in texture and easily broken; fractured surface fibrous and yellow in colour, reddish-brown in the centre (*1–4*).

Organoleptic properties

Odour, slight; taste, slightly bitter (*1–4*).

Microscopic characteristics

To be established according to national requirements. For guideline to microscopic characteristics, see Powdered plant material.

Powdered plant material

Yellow brown. Fragments of parenchyma cells containing small amounts of starch grains, spheroidal, 2–10 µm in diameter, hila distinct. Elongated, thick-walled stone cells. Reticulated vessels numerous, 24–72 µm in diameter. Phloem fibres scattered singly or in bundles, fusiform, 60–250 µm long, 9–33 µm in diameter, thick-walled, with fine pit-canals. Cork cells brownish-yellow, polygonal. Fragmented wood fibres, about 12 µm in diameter, with oblique pits (*1–4*).

General identity tests

Macroscopic and microscopic examinations (*1–4*), microchemical tests (*1, 4*) and high-performance liquid chromatography for the presence of baicalin (*2, 4*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Total ash

Not more than 6% (*1–4*).

Acid-insoluble ash

Not more than 1% (*3*).

Water-soluble extractive

Not less than 40% (*3*).

Alcohol-soluble extractive

Not less than 15% (*3*).

Loss on drying
Not more than 12% (*2*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*11*). For other pesticides, see the *European pharmacopoeia* (*11*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*12*).

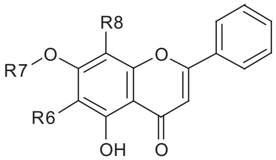
Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests
Chemical, foreign organic matter and sulfated ash tests to be established in accordance with national requirements.

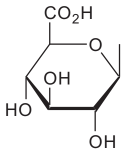
Chemical assays
Contains not less than 9.0% of baicalin determined by high-performance liquid chromatography (*4*). Other high-performance liquid chromatography methods are available (*2, 13*).

Major chemical constituents
The major constituents are flavonoids, chiefly baicalin (up to 14%) (*14*), baicalein (up to 5%) (*15*), wogonin (0.7%) (*15*) and wogonin-7-*O*-glucuronide (wogonoside, 4.0%) (*14, 16*). The structures of baicalin, baicalein and wogonin are presented below.



	R6	R7	R8
baicalein	OH	H	H
baicalin	OH	GlcA	H
wogonin	H	H	OCH_3

β-D-glucopyranuronosyl GlcA =



Medicinal uses

Uses supported by clinical data

None. Although clinical case reports suggest that Radix Scutellariae may stimulate the immune system and induce haematopoiesis (*17–19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Treatment of fever, nausea and vomiting, acute dysentery, jaundice, coughs, carbuncles and sores, and threatened abortion (*3, 4*).

Uses described in traditional medicine

Treatment of allergies, arteriosclerosis, diarrhoea, dermatitis and hypertension (*7*).

Pharmacology

Experimental pharmacology

Antihepatotoxic activity

Intragastric administration of 400.0 mg/kg body weight (bw) of an aqueous extract of Radix Scutellariae to rats prevented increases in the activities of liver enzymes, such as alkaline phosphatase, lactate dehydrogenase and alanine aminotransferase, induced by carbon tetrachloride or galactosamine (*20*). Baicalein, 185.0 µmol/l, inhibited the proliferation of cultured hepatic stellate cells (*21*). Baicalein, 10.0 µmol/l, also significantly ($P < 0.001$) decreased the incorporation of tritiated thymidine in cultured rat hepatic stellate cells stimulated with platelet-derived growth factor-B subunit homodimer or fetal calf serum (*22*).

Anti-inflammatory activity

External application of 0.5 mg/ear of a 50% ethanol extract of the roots to the ears of mice with ear oedema induced by 12-*O*-tetradecanoylphorbol-13-acetate or arachidonic acid significantly reduced inflammation ($P < 0.01$) (*23*). The anti-inflammatory effect of baicalein in treating chronic inflammation in rats with adjuvant-induced arthritis (median effective dose (ED_{50}) 120.6 mg/kg bw, intragastric route) was superior to that in carrageenan-induced footpad oedema (ED_{50} 200.0 mg/kg bw, intragastric route) (*24*). Baicalein also inhibited leukotriene C4 biosynthesis in vitro in rat resident peritoneal macrophages stimulated with calcium ionophore A23187, median inhibitory concentration (IC_{50}) 9.5 µm (*24*). Three flavonoids isolated from the roots, wogonin, baicalein and baicalin, 1.0 µg/ml, inhibited lipopolysaccharide-induced production of interleukin-1β in human gingival fibroblasts by 50% (*25*). The effects of nine

flavonoids, isolated from the roots, on adhesion molecule expression induced by interleukin-1β and tumour necrosis factor-α in cultured human umbilical vein endothelial cells were assessed. Baicalein only showed a dose-dependent inhibition of the induced expression of endothelial leukocyte adhesion molecule-1 and intracellular adhesion molecule-1, with 50% inhibition observed at concentrations of 0.23 µmol/l and 0.4 µmol/l, respectively. These data suggest that Radix Scutellariae may exert its anti-inflammatory effects through the inhibition of leukocyte adhesion to the endothelium (*26*). Baicalin has been shown to inhibit the binding of chemokines to human leukocytes and cells transfected with chemokine receptors. Coinjection of baicalin with CXC chemokine interleukin-8 into rat skin inhibited neutrophil infiltration elicited by interleukin-8 (*27*).

Antioxidant activity

The free-radical scavenging and antioxidant activities of baicalein, baicalin, wogonin and wogonoside were tested in vitro. Electron spin resonance results showed that baicalein and baicalin scavenged hydroxyl radical and alkyl radical in a dose-dependent manner, while wogonin and wogonoside had no effect. Baicalein and baicalin, 10 µmol/l, inhibited lipid peroxidation of rat brain cortex mitochondria induced by Fe(2+)/ascorbic acid or NADPH, while wogonin and wogonoside had effects only on NADPH-induced lipid peroxidation. In a study on cultured human neuroblastoma SH-SY5Y, baicalein and baicalin, 10 µmol/l, protected cells against hydrogen peroxide-induced injury (*28*). An aqueous extract of the roots or baicalein, 25–100 µmol/l, significantly ($P < 0.001$) attenuated ischaemia/reperfusion oxidative stress in cultured chick embryonic ventricular cardiomyocytes. Cell death due to ischaemia/reperfusion injury decreased from 47% to 26% in treated cells. After treatment of the cells with antimycin A, an extract of the roots decreased cell death to 23% in treated cells compared with 47% in untreated cells (*29*).

Pretreatment with ganhuangenin, isolated from the roots, suppressed the formation of phosphatidylcholine hydroperoxide initiated by the peroxyl-generating oxidant, 2,2'-azobis-2-aminopropane hydrochloride (*30*). Baicalein, 5.0–25.0 µmol/l, and wogonin, 5.0–50.0 µmol/l, inhibited lipopolysaccharide-induced nitric oxide generation in a macrophage-derived cell line, RAW 264.7 in a concentration-dependent manner. The same two compounds, 25.0 µmol/l, also inhibited protein expression of inducible nitric oxide synthase (*31*).

Antimicrobial activity

An aqueous or methanol extract of the roots, 200 µg/ml, elicited significant inhibition (> 90%) ($P < 0.01$) of the activity of human immuno-

deficiency virus type-1 protease (*32*). Baicalein inhibited the growth of *Fusarium oxysporum* and *Candida albicans* in vitro, minimum inhibitory concentrations 0.112 g/l and 0.264 g/l, respectively (*33*).

A hot aqueous extract of the roots inhibited the growth of *Alcaligenes calcoaceticus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus* at concentrations of 200.0–400.0 µg/ml but was not active against *Escherichia coli* in vitro at concentrations of up to 1600.0 µg/ml (*34*).

A hot aqueous extract of the roots, 0.25–1.0 µg/ml, inhibited the growth of *Actinomyces naeslundii*, *A. odontolyticus, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Bacteroides gingivalis, B. melaninogenicus* and *Streptococcus sanguis* (*35*).

Antitumour activity

The in vitro effects of baicalin on growth, viability, and induction of apoptosis in several human prostate cancer cell lines, including DU145, PC3, LNCaP and CA-HPV-10 were investigated. Baicalin inhibited the proliferation of prostate cancer cells but the responses were different in the different cell lines. DU145 cells were the most sensitive and LNCaP cells the most resistant. Baicalin caused a 50% inhibition of DU145 cells at concentrations of 150 µg/ml or higher. Inhibition of prostate cancer cell proliferation by baicalin was associated with induction of apoptosis (*36*). Baicalein inhibited the proliferation of estrogen receptor-positive human breast cancer MCF-7 cells in vitro, median effective concentration 5.3 µg/ml (*37*).

Antiviral activity

Baicalin inhibited retroviral reverse transcriptase activity in human immunodeficiency virus type 1 (HIV-1) activity in infected H9 cells, as well as HIV-1 specific core antigen p24 expression and quantitative focal syncytium formation on CEM-SS monolayer cells. Baicalin was a noncompetitive inhibitor of HIV-1 reverse transcriptase, IC_{50} 22.0 µmol/l. It also inhibited reverse transcriptase from Maloney murine leukaemia virus, Rous-associated virus type 2 and cells infected with human T-cell leukaemia virus type I (HTLV-I) (*38*). A flavone, 5,7,4'-trihydroxy-8-methoxyflavone, isolated from the roots, inhibited the activity of influenza virus sialidase but not mouse liver sialidase in vitro (*39*). The compound also had anti-influenza virus activity in Madin-Darby canine kidney cells, in the allantoic sac of embryonated eggs (IC_{50} 55.0 µmol/l) and in vivo in mice (*39–41*). The compound, 50.0 µmol/l, was also shown to reduce the single-cycle replication of mouse-adapted influenza virus A/PR/8/34 in Madin-Darby canine kidney cells by inhibiting the fusion of the virus

with endosome/lysosome membrane and the budding of the progeny virus from the cell surface in the virus infection cycle (*42*). Baicalein produced a concentration-dependent inhibition of HTLV-I replication in infected T and B cells, as well as inhibiting the activity of reverse transcriptase in cells infected with HTLV-I (*43*). The mechanism by which baicalin exerts its anti-HIV-1 activities appears to involve the binding of baicalin to form complexes with selected cytokines and attenuates their ability to bind and activate receptors on the cell surface. Baicalin also binds to the HIV-1 envelope proteins and the cellular CD4 and chemokine co-receptors, thereby blocking HIV-1 entry into the cell (*44*).

Central nervous system activity

Four chemical constituents isolated from the roots bound to the benzodiazepine-binding site of the γ-aminobutyric acid A receptor as follows; wogonin (2.03 µmol/l) > baicalein (5.69 µmol/l) > scutellarein (12.00 µmol/l) > baicalin (77.00 µmol/l) (*45*). Results of a benzodiazepine-binding assay showed that three flavones, baicalein, oroxylin A and skullcapflavone II, from an aqueous extract of the roots bound to the benzodiazepine-binding site with Ki values of 13.1 µmol/l, 14.6 µmol/l and 0.36 µmol/l, respectively (*46*).

Intragastric administration of an aqueous extract of the roots (dose not specified) to rats produced an increase in cutaneous vasodilation resulting in a fall in rectal temperature. No changes in metabolic rate or respiratory evaporative heat loss were observed (*47*).

Enzyme inhibition

Baicalin inhibited the activity of aldose reductase isolated from bovine testes, inhibitory concentration 5.0 µg/ml (*48*).

Immunological effects

Treatment of mouse peritoneal macrophages with an aqueous extract of the roots, 0.1–100.0 µg/ml, following treatment with recombinant interferon-γ, resulted in a significant ($P < 0.05$) increase in the production of nitric oxide (*49*). However, a decoction of the roots inhibited nitric oxide production induced by lipopolysaccharide treatments of murine macrophages, IC_{50} 20.0 µg/ml (*50*).

Platelet aggregation inhibition

A 1-butanol, chloroform or ethyl acetate extract of the roots, 400.0 µg/ml, inhibited platelet-activating factor binding to rabbit platelets in vitro (*51*). An aqueous or hexane extract of the roots, 5.0 mg/ml, inhibited platelet aggregation induced by arachidonic acid, adenosine diphosphate and collagen in rat platelets in vitro (*52, 53*). Baicalein dose-dependently

inhibited production of plasminogen activator inhibitor-1 in cultured human umbilical vein endothelial cells induced by treatment with thrombin and thrombin receptor agonist peptide, IC_{50} values 6.8 µmol/l and 3.5 µmol/l, respectively (*54*).

Smooth muscle effects

The vascular effect of purified baicalein was assessed in isolated rat mesenteric arteries. Baicalein exerted both contractile and relaxant effects on the thromboxane receptor agonist U46619-, phenylephrine- or high potassium-contracted endothelium-intact arteries. In endothelium-denuded arteries, the contractile response to baicalein, 0.3–10 µmol/l, was absent while the relaxant response to baicalein, 30–300.0 µmol/l, remained. Pretreatment with 100.0 µmol/l of NG-nitro-L-arginine (L-NNA) abolished the effect. Pretreatment with baicalein, 3–10.0 µmol/l, attenuated relaxation induced by acetylcholine or calcium ionophore A23187. At low concentrations, baicalein caused a contractile response and inhibited the endothelium-dependent relaxation, probably through inhibition of endothelial nitric oxide formation/release. At higher concentrations, baicalein relaxed the arterial smooth muscle, partially through inhibition of protein kinase C (*55*).

Toxicology

Intragastric administration of 10.0 g/kg bw of a decoction of the roots or intravenous administration of 2.0 g/kg bw of an ethanol extract to rabbits induced sedation but no toxic effects were observed (*17*). Intravenous administration of 2.0 g/kg bw of an aqueous extract of the roots to rabbits initially produced sedation. However, 8–12 hours later all the animals died. When the dose was decreased to 1.0 g/kg bw no deaths occurred. The median oral lethal dose (LD_{50}) of a 70% methanol extract of the roots in mice was > 2.0 g/kg (*56*).

Intragastric administration of 12.0–15.0 g/kg bw of an aqueous extract of the roots to dogs caused emesis but no other toxic effects. Oral administration of 4.0–5.0 g/kg bw of the same extract three times per day for 8 weeks to dogs did not cause any toxic effects. The subcutaneous LD_{50} in mice was 6.0 g/kg bw for an ethanol extract of the roots, 6.0 g/kg bw for baicalin and 4.0 g/kg bw for wogonin (*17*). The intraperitoneal LD_{50} of baicalin in mice was 3.1 g/kg bw (*17*).

Clinical pharmacology

Chemotherapy of patients with lung cancer is associated with a decrease in immune function owing to a decrease in the relative number of T-lymphocytes. Administration of a dry extract of the roots to cancer patients

receiving chemotherapy produced a tendency towards an increase in lymphocytes. The immunoregulation index in this case was approximately twice the background values during the whole period of investigation. The inclusion of the roots in the therapeutic regimen promoted an increase in the level of immunoglobulin A and stabilized the concentration of immunoglobulin G (no further details available) (*19*).

A decoction of the roots was used to treat upper respiratory infections in children up to 5 years old and younger. The dose administered was 6.0 ml for children under the age of 1 year, and 8.0–10.0 ml for children up to 5 years of age. Of 63 cases (51 with respiratory tract infections, 11 with acute bronchitis, and one with acute tonsillitis), 51 showed benefit, and body temperature normalized after 3 days of treatment (*17*).

Haematopoiesis was studied in 88 patients with lung cancer during antitumour chemotherapy given in combination with a dry extract of the roots. Oral administration of the roots induced haematopoiesis, intensification of bone-marrow erythro- and granulocytopoiesis and an increase in the content of circulating precursors of erythroid and granulomonocytic colony-forming units (*18*).

Adverse reactions

Rare gastrointestinal discomfort and diarrhoea are associated with oral administration of Radix Scutellariae (*17*). Although liver damage due to administration of the roots has been suggested (*57*), no direct correlations of ingestion of the roots to any published cases of liver damage have been published.

Contraindications

Owing to possible teratogenic and mutagenic effects (*58*, *59*), and a lack of safety data, use of Radix Scutellariae is contraindicated during pregnancy and nursing and in children under the age of 12 years.

Warnings

No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous extract of Radix Scutellariae, 40.0 mg/plate, was not mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 (*59, 60*). However, intraperitoneal administration of 4.0 mg/

kg bw of the aqueous extract to mice, equal to 10–40 times the amount used in humans, was mutagenic (*59*).

Pregnancy: teratogenic effects

Intragastric administration of 500.0 mg/kg bw of a 70% methanol extract of the roots daily to rats starting on the 13th day of pregnancy had no teratogenic or abortifacient effects (*56*). An aqueous extract of the roots, 24.98 g/kg bw, given by intragastric administration to pregnant rats on days 8–18 of pregnancy was teratogenic (*58*).

Pregnancy: non-teratogenic effects

Intragastric administration of 24.98 g/kg bw of an aqueous extract of the roots to pregnant rabbits on days 8–18 of pregnancy had no abortifacient effects (*58*). A methanol extract of the roots, 1.0 mg/ml, inhibited oxytocin-induced contractions in isolated rat uterus (*61*).

Nursing mothers

See Contraindications.

Paediatric use

See Contraindications.

Other precautions

No information available on general precautions or on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms

Dried roots, extracts, infusions and decoctions. Store in a well closed container in a cool, dry place, protected from moisture (*4*).

Posology

(Unless otherwise indicated)

Daily dose: 3–9 g of dried roots as an infusion or decoction (*4*).

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Radix cum Herba Taraxaci

Definition

Radix cum Herba Taraxaci consists of the entire plant of *Taraxacum officinale* Weber ex Wiggers (Asteraceae) (*1–3*).[1]

Synonyms

For *Taraxacum officinale*: *Leontodon officinale* With., *L. taraxacum L. Taraxacum officinale* (With.) Wigg., *T. dens leonis* Desf., *T. vulgare* Schrank, (*6*).

Selected vernacular names

Ackerzichorie, amargon, blowball, Butterblume, cankerwort, capo di frate, chicoria amarga, cicoria sarvatica, cicouureya de la bonne, cicoureya deis prats, dandelion, dent-de-lion, dente di leone, dhudal, diente de leon, dhorsat al ajouz, dudhi, engraissa-porc, florion d'or, gol ghased, Gemeiner Löwenzahn, gobesag, Irish daisy, hindabaa beri, hokgei, kanphul, kanphuli, kasni sahraii, Kettenblume, khass berri, Kuhblume, lagagna, laiteron, lechuguilla, lion's tooth, Löwenzahn, maaritpauncin, marrara, milk gowan, min-deul-rre, monk's head, mourayr, mourre de por, mourre de pouerc, oduwantschiki, paardebloem, patalagagna, peirin, Pfaffendistel, Pfaffenröhrlein, Pferdeblume, pilli-pilli, piochoublit, piss-a-bed, pissa-chin, pissanliech, pissenlit, poirin, po-kong-young, porcin, pu gong ying, puffball, pugongying, Pusteblume, ringeblume, salatta merra, sanalotodo, saris berri, seiyo-tanpopo, sofione, srissi, tarakh-chaqoune, tarkhshaquin, tarassaco, taraxaco, telma retaga, Wiesenlattich, witch gowan, yellow gowan (*4–10*).

Geographical distribution

Taraxacum officinale is indigenous to the northern hemisphere (*11*). *T. mongolicum, T. sinicum* and related species are found in the Korean peninsula and China (*4, 5*).

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[1] *Taraxacum mongolicum* Hand.-Mazz. and *T. sinicum* Kitag. are also recognized in the *Pharmacopoeia of the People's Republic of China* (*4*) and the *Pharmacopoeia of the Republic of Korea* (*5*).

Description

A perennial herb consisting of an underground, long, straight, tapering, fleshy brown root, which is continued upward as a simple or branched rhizome. From the rhizome arises a rosette of bright-green runcinate leaves and later, from the centre of the rosette, a hollow scape, 6–30 cm high bearing on its summit a broad orange-yellow head of ligulate flowers. Fruits are fusiform, greenish-brown achenes, terminating in a slender stalk crowned by a silky, spreading pappus, and borne on a globular fruiting head (*12*).

Plant material of interest: dried whole plants

General appearance

A crumpled and rolled mass. Roots conical, frequently curved, tapering, often broken into irregular pieces, externally brown. Root stock with brown or yellowish-white hairs. Leaves basal, frequently crumpled and broken; when whole, oblanceolate, greenish-brown or dark green with a pronounced midrib; apex acute or obtuse; margins lobate or pinnatifid. Pedicels one or more, each with a capitulum; involucre several rows, the inner row relatively long; corolla yellowish-brown or pale yellowish-white (*1, 4, 5*).

Organoleptic properties

Odour, slight; taste, slightly bitter (*1, 11*).

Microscopic characteristics

Epidermal cells on both leaf surfaces have sinuous anticlinal walls, cuticle striations distinct or sparsely visible. Both leaf surfaces bear non-glandular hairs with three to nine cells, 17–34 µm in diameter. Stomata, occurring more frequently on the lower surface, anomocytic or anisocytic, with three to six subsidiary cells. Mesophyll contains fine crystals of calcium oxalate. Transverse section of root shows cork with several layers of brown cells. Phloem broad, groups of laticiferous tubes arranged in several interrupted rings. Xylem relatively small, with indistinct rays, vessels large, scattered. Parenchymatous cells contain inulin (*1*).

Powdered plant material

Greenish yellow. Large root parenchymatous cells, brown reticulate vessels and tracheids and non-lignified fibres. Leaf fragments with sinuous, anticlinal-walled epidermal cells and a few anomocytic stomata. Numerous narrow annular thickened vessels and fragments of brown laticiferous tissues (*1*).

General identity tests

Macroscopic and microscopic examinations (*1, 4, 5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 17% (*3*).

Water-soluble extractive

Not less than 30% (*3*).

Loss on drying

Not more than 11% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

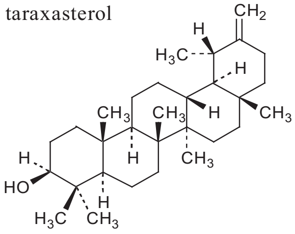
Chemical assays

To be established in accordance with national requirements.

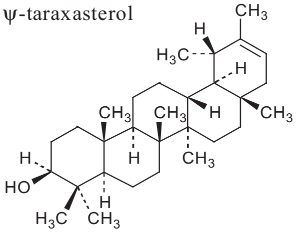
Major chemical constituents

The characteristic constituents are sesquiterpenes, including the bitter eudesmanolides tetrahydroridentin B and taraxacolide β-D-glucopyranoside; and the germacranolides, taraxinic acid β-D-glucopyranoside and 11,13-dihydrotaraxic acid β-D-glucopyranoside. Also present are the *p*-hydroxyphenylacetic acid derivative, taraxacoside; the triterpenes, taraxasterol, ψ-taraxasterol and taraxerol; and inulin (2–40%) (*4, 10, 11*). Representative structures are presented below.

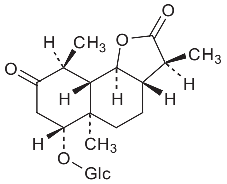
taraxasterol



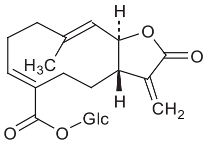
ψ-taraxasterol



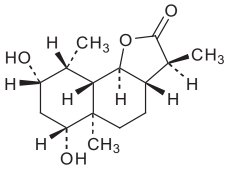
taraxacolide β-D-glucoside



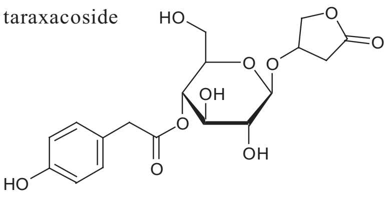
taraxinic acid β-D-glucosyl ester

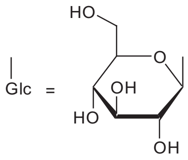


tetrahydroridentin B



taraxacoside





β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

No information available.

Uses described in pharmacopoeias and well established documents

To stimulate diuresis (*2, 5*), increase bile flow and stimulate appetite, and for treatment of dyspepsia (*2*).

Uses described in traditional medicine

As a galactagogue, laxative and tonic. Treatment of boils and sores, diabetes, fever, inflammation of the eye, insomnia, sore throat, lung abscess, jaundice, rheumatism and urinary tract infections (*10*).

Pharmacology

Experimental pharmacology

Anti-inflammatory and analgesic activity

External applications of 2.0 mg/ear of a methanol extract of the dried leaves to mice reduced ear inflammation induced by 12-*O*-tetradecanoylphorbol-13-acetate (*16*). Intragastric administration of 1.0 g/kg body weight (bw) of a 95% ethanol extract of the whole plant to mice inhibited benzoquinone-induced writhing (*17*). Intraperitoneal administration of 100.0 mg/kg bw of a 95% ethanol extract of the whole plant to mice inhibited carrageenan-induced footpad oedema by 42%, and reduced pain as measured by the hot-plate test and benzoquinone-induced writhing (*17*). Intragastric administration of 100.0 mg/kg bw of an 80% ethanol extract of the dried roots to rats inhibited carrageenan-induced footpad oedema by 25%, compared with 45% inhibition resulting from administration of 5.0 mg/kg bw of indometacin (*18*).

Antimicrobial activity

A 95% ethanol extract of the dried aerial parts, 1.0 mg/ml, did not inhibit the growth of *Bacillus globifer*, *B. mycoides, B. subtilis, Escherichia coli, Fusarium solani, Klebsiella pneumoniae, Penicillium notatum, Proteus morganii, Pseudomonas aeruginosa, Salmonella gallinarum, Serratia marcescens, Staphylococcus aureus, Mycobacterium smegmatis* or *Candida albicans* in vitro (*19, 20*). No antibacterial effects were observed using a 50% ethanol extract of the whole plant, 50 µl/plate, against *Escherichia coli, Salmonella enteritidis, Salmonella typhosa, Shigella dysenteriae* or *Shigella flexneri* (*21*).

Antiulcer activity

Intragastric administration of 2.0 g/kg bw of an aqueous extract of the whole plant to rats protected the animals against ethanol-induced gastric ulceration. A methanol extract, however, was not active (*22*).

Choleretic activity

Intragastric administration of an aqueous or 95% ethanol extract of the whole plant (dose not specified) to rats increased bile secretion by 40% (*23*).

Diuretic activity

Intragastric administration of 8.0–50.0 ml/kg bw of a 95% ethanol extract of the whole plant to rats induced diuresis and reduced body weight (*24*). Intragastric administration of 0.1 ml/kg bw of a 30% ethanol extract of the whole plant to mice induced diuresis (*25*). However, intragastric

administration of 50.0 mg/kg bw of a chloroform, methanol or petroleum ether extract of the roots to mice did not consistently increase urine output (*26*).

Hypoglycaemic activity
Intragastric administration of a 50% ethanol extract of the whole plant to rats, 250.0 mg/kg bw, or rabbits, 1.0 g/kg bw, reduced blood glucose concentrations (*27*). However, intragastric administration of 2.0 g/kg bw of the powdered whole plant to rabbits did not reduce blood sugar concentrations in alloxan-induced hyperglycaemia (*28*). Intragastric administration of 25.0 mg/kg bw of an aqueous extract of the dried root to mice reduced glucose-induced hyperglycaemia (*29, 30*). However, a decoction or 80% ethanol extract of the dried roots had no effect (*30*).

Immunological effects
Intragastric administration of 3.3 g/kg bw of an aqueous extract of the whole plant to mice daily for 20 days significantly ($P < 0.01$) decreased cyclophosphamide-induced immune damage (*31*). Treatment of scalded mice with suppressed immune functions with an aqueous extract of the whole plant (dose and route not specified) stimulated the immune response (*32*). Nitric oxide synthesis inhibition induced by cadmium in mouse peritoneal macrophages stimulated with recombinant interferon-γ and lipopolysaccharide was counteracted by treatment of the cells with an aqueous extract of the whole plant, 100 µg/ml. The results were mainly dependent on the induction of tumour necrosis factor-α (TNF-α) secretion stimulated by the aqueous extract (*33*). Treatment of primary cultures of rat astrocytes with an aqueous extract of the whole plant, 100.0 µg/ml, inhibited TNF-α production induced by lipopolysaccharide and substance P. The treatment also decreased the production of interleukin-1 in astrocytes stimulated with lipopolysaccharide and substance P. The study indicated that Radix cum Herba Taraxaci may inhibit TNF-α production by inhibiting interleukin-1 production, thereby producing anti-inflammatory effects (*34*). Treatment of mouse peritoneal macrophages with an aqueous extract of the whole plant, 100 µg/ml, after treatment of the cells with recombinant interferon-γ, resulted in increased nitric oxide synthesis owing to an increase in the concentration of inducible nitric oxide synthase. The results were dependent on the induction of TNF-α secretion by Radix cum Herba Taraxaci (*35*).

Toxicology
The intraperitoneal median lethal dose (LD_{50}) of a 95% ethanol extract of the whole plant in rats was 28.8 mg/kg bw (*24*). In rats, the maximum

tolerated dose of a 50% ethanol extract of the whole plant administered by the intraperitoneal route was 500.0 mg/kg bw (*27*). No visible signs of toxicity were observed in rabbits after intragastric administration of the powdered whole plant at doses of 3–6 g/kg bw per day for up to 7 days (*36*).

Clinical pharmacology
No information available.

Adverse reactions
Allergic reactions including anaphylaxis and pseudoallergic contact dermatitis have been reported (*37–40*). Cross-reactivity has been reported in individuals with an allergy to the pollen of other members of the Asteraceae (*41*).

Contraindications
Radix cum Herba Taraxaci is contraindicated in obstruction of the biliary or intestinal tract, and acute gallbladder inflammation. In case of gallbladder disease, Radix cum Herba Taraxacum should only be used under the supervision of a health-care professional (*2*).

Warnings
May cause stomach hyperacidity, as with all drugs containing amaroids (*2*).

Precautions
Drug interactions
A decrease in the maximum plasma concentration of ciprofloxacin was observed in rats treated with concomitant oral administration of 2.0 g/kg bw of an aqueous extract of the whole plant and 20.0 mg/kg bw of ciprofloxacin (*42*).

Carcinogenesis, mutagenesis, impairment of fertility
No effects on fertility were observed in female rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (*43*).

Pregnancy: teratogenic effects
No teratogenic or embryotoxic effects were observed in the offspring of rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (*43*).

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried whole plant, native dry extract, fluidextract and tincture (*1, 2*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose: 3–4 g of cut or powdered whole plant three times; decoction, boil 3–4 g of whole plant in 150 ml of water; infusion, steep 1 tablespoonful of whole plant in 150 ml of water; 0.75–1.0 g of native dry extract 4:1 (w/w); 3–4 ml fluidextract 1:1 (g/ml) (*2*); 5–10 ml of tincture (1:5 in 45% alcohol) three times (*1*).

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Semen Trigonellae Foenugraeci

Definition

Semen Trigonellae Foenugraeci consists of the dried ripe seeds of *Trigonella foenum-graecum* L. (Fabaceae) (*1–7*).

Synonyms

Buceras foenum-graecum (L.) All., *Foenum-graecum officinale* Moench, *F. officinale* Moench var. *cultum* Alef., *F. sativum* Med., *Folliculigera graveolens* Pasq., *Tels foenum-graecum* (L.) Kuntze, *Trigonella foenum-graecum* L. subsp. *culta* (Alef.) Gams, *T. graeca* St Lag. and *T. jemenensis* (Serp.) Sinsk. (*8*). Fabaceae are also known as Leguminosae.

Selected vernacular names

Alholvabockshorn, bahubeeja, bahupatrika, bhaji, Bockshornklee, bothinee, boukeros, bukkehorn, chamliz, chanbalid, chanbalila, chanbalit, chandrika, chilebe, deepanee, el halbah, fariqua, feenugreek, fenacho, fenigrek, fenogreco, fenogreco, fénugrec, fenugreek, fenugriego, fieno-greco, foenugreek, fumugrec, gandhaphala, goat's horn, Greek hay, halba, halbet, hay trigonella, helba, henogriego, hilba, hinojogriego, hoolbah, hula-pa, hulba, huluba, hulupa, jyoti, kelabat, kelabet, klabet, koroha, kozieradka pospolita, Kuhhornklee, kunchika, l-helba, maithi, maithy, mathi, menle, mentepale, menthiam, menthi, menti-kuroa, methi, methika, methiky, methini, methra, methuka, methisak, mentikoora, mentulu, methun, methy, mitha, monte soffu, munichhada, pe-nam-ta-zi, penan-ta, peetabeeja, samli, schöne Margret, schöne Marie, senegré, shamlit, shamlid, shamlitz, shanbalileh, shandalid, thenthya, tifidas, tilis, uluhaal, uluva, vendayam, venthiam, ventayam (*1, 4, 8–12*).

Geographical distribution

Indigenous to the Mediterranean region, China, India and Indonesia. Cultivated in these countries (*5, 13*).

Description
Annual aromatic herb, up to 60 cm high with a well developed taproot and much branched roots. Stem solitary or basally branched, terete, slightly pubescent, green to purple. Leaves petiolate, alternate, trifoliolate; stipules triangular, small, adnate to the petiole. Rachis short. Leaflets obovate or oblong, 1.5–4.0 cm long, 0.5–2.0 cm wide, upper part of margin denticulate. Flowers whitish, solitary, axillary, subsessile, 12–15 mm long. Calyx campanulate, finely pubescent, tube 4.5 mm long, with five lobes. Pistil with sessile ovary, glabrous style and capitate stigma. Fruits straight to occasionally sickle-shaped, linear pods, glabrous, with fine longitudinal veins, terminating in a beak 2–3 cm long. Seeds oblong-rhomboidal, 3–5 mm long and 2–3 mm wide, with a deep furrow dividing each into two unequal lobes, with rounded corners, rather smooth, brownish (*11*).

Plant material of interest: dried ripe seeds
General appearance
Oblong-rhomboidal, 3.0–5.0 mm long, 2.0–3.0 mm wide, 1.5–2.0 mm thick, with rounded corners, rather smooth. Yellowish-brown to reddish-brown, with a deep furrow dividing each seed into two unequal lobes, and a deep hilum at the intersection of the two furrows. Texture hard, not easily broken. Testa thin, endosperm translucent and viscous; cotyledons two, pale yellow, radicle curved, plump and long (*1, 6, 7, 11*).

Organoleptic properties
Odour: characteristic, aromatic; taste: slightly bitter (*1, 2, 6, 7*).

Microscopic characteristics
Transverse section shows an epidermis of palisade cells, one layer, with thick cuticle and thick lamellated walls, and a relatively large lumen at the lower part. Longitudinal pit-canals fine and close. Subepidermal layer of basket-like cells, with bar-like thickening on the radial walls, followed by a parenchymatous layer. Endosperm of several layers of polyhedral cells with stratified mucilaginous contents and thickened walls. Cotyledons of parenchymatous cells containing fixed oil and aleurone grains up to 15 µm in diameter (*1, 2, 7*).

Powdered plant material
Yellowish-brown showing fragments of the testa in sectional view with thick cuticle covering epidermal cells, with an underlying hypodermis of large cells, narrower at the upper end and constricted in the middle, with bar-like thickenings of the radial walls. Yellowish-brown fragments of the epidermis

in surface view, composed of small polygonal cells with thickened and pitted walls, frequently associated with the hypodermal cells, circular in outline with thickened walls. Fragments of the hypodermis viewed from below, composed of polygonal cells with bar-like thickenings extending to the upper and lower walls. Parenchyma of the testa with elongated, rectangular cells with slightly thickened walls. Fragments of endosperm with irregularly thickened, sometimes elongated cells, containing mucilage (*1, 2, 6*).

General identity tests

Macroscopic and microscopic examinations (*1, 2, 5–7, 11*), microchemical tests (*5*), and thin-layer chromatography for the presence of trigonelline (*5, 6*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Foreign organic matter

Not more than 2% (*1, 2, 4, 6*).

Total ash

Not more than 5% (*3, 6*).

Acid-insoluble ash

Not more than 2% (*1, 2, 5*).

Water-soluble extractive

Not less than 35% (*5*).

Alcohol-soluble extractive

Not less than 5% (*4*).

Loss on drying

Not more than 12% (*6*).

Swelling index

Not less than 6 (*3, 6*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the *European pharmacopoeia*

(*15*) and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

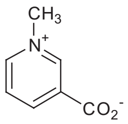
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests
Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays
To be established in accordance with national requirements.

Major chemical constituents
Semen Trigonellae Foenugraeci is rich in mucilage (25–45%) and contains a small amount of essential oil (0.01%) and a variety of secondary metabolites, including protoalkaloids, trigonelline (up to 0.37%), choline (0.05%); saponins (0.6–1.7%) derived from diosgenin, yamogenin, tigogenin and other compounds; sterols including β-sitosterol; and flavonoids, among which are orientin, isoorientin and isovitexin (*8, 12, 13, 17*). The structure of trigonelline is presented below.

trigonelline



Medicinal uses
Uses supported by clinical data
As an adjunct for the management of hypercholesterolaemia, and hyperglycaemia in cases of diabetes mellitus (*18–21*). Prevention and treatment of mountain sickness (*22*).

Uses described in pharmacopoeias and well established documents
Internally for loss of appetite, and externally as a poultice for local inflammations (*23*). Treatment of pain, and weakness and oedema of the legs (*7*).

Uses described in traditional medicine

As an aphrodisiac, carminative, diuretic, emmenagogue, emollient, galactagogue and tonic (*12, 23*). Treatment of abdominal colic, bronchitis, diarrhoea, eczema, gout, indigestion, dropsy, fever, impotence, chronic cough, liver disorders, wounds and the common cold (*5, 12*).

Pharmacology

Experimental pharmacology

Antihypercholesterolaemic activity

Intragastric administration of 30.0 g/kg body weight (bw) or 50.0 g/kg bw of an ethanol extract of Semen Trigonella daily for 4 weeks to hypercholesterolaemic rats reduced plasma cholesterol levels by 18% and 25%, respectively. Treatment also lowered liver cholesterol concentrations in these animals (*24*).

Antihyperglycaemic activity

Oral administration of 250.0 mg of an aqueous or methanol extract of seeds daily to normal and diabetic rats significantly reduced blood glucose levels after eating or the administration of glucose ($P < 0.05$) (*25*). Intragastric administration of 250.0 mg of an ethanol extract of the seeds daily for 28 days reduced blood glucose levels in rats with streptozotocin-induced diabetes (*26*), and increased the number of beta cells and the diameter of pancreatic islet cells (*27*).

Intragastric administration of 2.0 g/kg bw or 8.0 g/kg bw of the seeds to rats with or without alloxan-induced diabetes produced a significant decrease ($P < 0.05$) in blood glucose (*28*). Intragastric administration of a single dose of 0.5 ml of a decoction or 200.0 mg/kg bw of an ethanol extract of the seeds to mice with or without alloxan-induced diabetes reduced serum glucose levels (*29*). Chronic administration of a high-fibre defatted extract of the seeds in the diet (content not specified) to dogs with alloxan-induced diabetes for 21 days decreased hyperglycaemia and glucosuria, and reduced the high levels of plasma glucagon and somatostatin (*30*). Intragastric administration of an acetone extract of the seeds (dose not specified) to fasted rats antagonized hyperglycaemia induced by cadmium or alloxan but had no effect on normal animals (*31*).

Anti-implantation activity

Extracts of the seeds (undefined) exhibited anti-implantation effects (approximately 30%) in rats when administered orally in a single dose of 25.0 mg/kg bw from day 1 to day 10 of pregnancy. The average number of fetal implants was significantly decreased ($P < 0.05$) (*32*).

Antioxidant activity

Administration of 2 g/kg bw of the seeds in the diet of rats with alloxan-induced diabetes lowered lipid peroxidation, increased the glutathione and β-carotene concentrations and reduced the α-tocopherol content in the blood (*33*).

Gastrointestinal effects

Administration of 10.0 mg/300 g bw, 12.5 mg/300 g bw or 100.0 mg/300 g bw of a steroid-enriched extract of the seeds per day in the diet to rats with or without streptozotocin-induced diabetes significantly ($P < 0.01$) increased food intake and the motivation to eat. The treatment also decreased total plasma cholesterol without changing the level of triglycerides (*34, 35*).

Toxicology

Intragastric administration of a debitterized powder of the seeds to mice and rats, 2.0 g/kg bw and 5.0 g/kg bw respectively, did not produce any signs of acute toxicity or mortality. In a 90-day subchronic study, weanling rats were fed with the powder in the diet, 1.0%, 5.0% or 10.0%. Terminal autopsy showed no signs of organ damage, increase in liver enzymes, haematological changes or toxicity (*36*).

Administration of a saponin fraction from the seeds by intramuscular injection, by intraperitoneal injection, 50.0 mg/kg bw per day, or in drinking-water, 500.0 mg/kg bw, to chicks for 21 days decreased body weight and increased liver enzymes. Pathological changes observed included fatty cytoplasmic vacuolation in the liver, necrosis of hepatocytes with lymphocytic infiltration, epithelial degeneration of the renal tubules, catarrhal enteritis, myositis and peritonitis (*37*).

Intragastric administration of an aqueous or 95% ethanol extract of the seeds (dose not specified) stimulated uterine contractions in healthy and pregnant rats, mice and guinea-pigs (*38, 39*). In vitro, a 50% ethanol extract of the seeds, 2%, had spermicidal effects and immediately immobilized human sperm on contact (*40, 41*).

Clinical pharmacology

Numerous clinical studies have assessed the effects of the seeds on serum cholesterol and glucose levels in patients with mild to moderate hypercholesterolaemia or diabetes (*18–21, 42*).

In a crossover trial, the effects of a powder of the seeds of *Momordica charantia* (MC) or T*rigonella foenum-graecum* (TF), or a combination of the two on total serum cholesterol, high-density-lipoprotein cholesterol, low-density-lipoprotein cholesterol, very-low-density-lipoprotein

cholesterol and triglycerides were investigated in 20 hypercholesterolaemic non-insulin dependent diabetes mellitus patients. Each subject was given 4.0 mg of MC, 50.0 mg of TF or a 50% combination of the two per day for 14 days. Mean serum total cholesterol was 271.4 mg/dl at the start of the study, and was significantly ($P < 0.001$) decreased to 234.1 mg/dl, 230.6 mg/dl and 225.8 mg/dl after MC, TF or the combination treatment, respectively. All other lipid parameters were also significantly decreased ($P < 0.001$) (*21*).

In a placebo-controlled clinical trial, the effect of ginger and Semen Trigonella on blood lipids, blood sugar, platelet aggregation, and fibrinogen and fibrinolytic activity was investigated. The subjects included healthy volunteers and patients with coronary artery disease and/or insulin-dependent diabetes mellitus. Healthy subjects treated with 2.5 g of the seeds twice per day for 3 months showed no changes in blood lipids and blood sugar (either fasting or after eating). However, in diabetic patients with cardiovascular disease, the treatment significantly ($P < 0.001$) decreased total cholesterol and triglycerides, without affecting high-density-lipoprotein concentrations. In diabetic patients without cardiovascular disease, the seeds reduced blood sugar levels in both fasting and non-fasting subjects, although the treatment was not effective in patients with severe diabetes (*20*).

A prescribed diet with or without the seeds, 25.0 g/day, was given to 60 patients with non-insulin dependent diabetes for a 7-day preliminary period and then for a 24-week trial. The diet containing the seeds lowered fasting blood glucose and improved glucose tolerance. The 24-hour urinary sugar excretion was significantly reduced ($P < 0.001$), and glycosylated haemoglobin was significantly reduced ($P < 0.001$) by week 8 of the trial (*19*).

The effect of the seeds on blood glucose and the serum lipid profile was assessed in 10 patients with insulin-dependent (type I) diabetes patients. Isocaloric diets with or without the seeds, 100.0 g/day, were administered in a randomized manner for 10 days. The diet containing the seeds significantly reduced ($P < 0.001$) fasting blood sugar and improved glucose tolerance tests. There was a 54% reduction in 24-hour urinary glucose excretion. Serum total cholesterol, low-density-lipoprotein cholesterol, very-low-density-lipoprotein cholesterol and triglycerides were also reduced. The high-density-lipoprotein cholesterol concentrations remained unchanged (*18*).

In a long-term study, 60 patients with diabetes ingested 25.0 g of seeds per day for 24 weeks. No changes in body weight or levels of liver enzymes, bilirubin or creatinine were observed, but blood urea levels decreased after 12 weeks. No evidence of renal or hepatic toxicity was observed (*43*).

Adverse reactions

Allergic reactions to the seeds following ingestion or inhalation have been reported (*44, 45*). These reactions range from rhinorrhoea, wheezing, fainting and facial angioedema (*45*). A 5-week-old infant had a 10-minute episode of unconsciousness after drinking a tea prepared from the seeds; however, upon medical examination, all tests were normal (*46*).

Contraindications

Semen Trigonellae Foenugraeci is contraindicated in cases of allergy to the plant material. Owing to its stimulatory effects on the uterus, the seeds should not be used during pregnancy (*39*).

Warnings

No information available.

Precautions

Drug interactions

Owing to its effect on blood glucose levels in diabetic patients, Semen Trigonellae Foenugraeci should only be used in conjunction with oral antihyperglycaemic agents or insulin under the supervision of a health-care professional.

Carcinogenesis, mutagenesis, impairment of fertility

An aqueous and a chloroform/methanol extract of the seeds were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 (*47, 48*). The extracts were also not mutagenic in pig kidney cells or in trophoblastic placental cells (*47*).

Pregnancy: non-teratogenic effects

See Contraindications.

Other precautions

No information available on general precautions or on precautions concerning drug and laboratory test interactions; teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms

Dried seeds, extracts, fluidextracts and tinctures (*23*). Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Average daily dose. Internal use, cut or crushed seed, 6 g, or equivalent of preparations; infusion, 0.5 g of cut seed macerated in 150 ml cold water for 3 hours, several cups; fluidextract 1:1 (g/ml), 6 ml; tincture 1:5 (g/ml), 30 ml; native extract 3–4:1 (w/w), 1.5–2 g. External use: bath additive, 50 g of powdered seed mixed with 250 ml water, added to a hot bath; poultice, semi-solid paste prepared from 50 g of powdered seed per litre of hot water, apply locally (*23*).

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Cortex Uncariae

Definition

Cortex Uncariae consists of the dried stem bark of *Uncaria tomentosa* (Willd.) DC. (Rubiaceae).

Synonyms

Nauclea aculeata auct. Non Willd., *N. cinchoneae* DC, N. polycephala A. Rich., *N. tomentosa* Willd., *Ourouparia polycephala* Baill., *Uncaria surinamensis* Miq., *U. tomentosa* DC, *Uruparia tomentosa* (Willd.) O. Kuntze (*1, 2*).

Selected vernacular names

Bejuco de agua, cat's claw, cat's thorn, deixa, garabato, garabato amarillo, garabato colorado, garra gavilán, hank's clay, jipotatsa, Katzenkralle, kug kukjaqui, micho-mentis, paotati-mosha, paraguyayo, rangaya, saventaro, toroñ, tsachik, tua juncara, uña de gato, uña de gato de altura, uncucha, unganangi, unganangi, unha de gato (*1–5*).

Geographical distribution

Indigenous to Central America and northern South America including Belize, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Nicaragua, Peru, Suriname, Trinidad and Tobago, and Venezuela, with Peru being the main source (*1, 6, 7*).

Description

A scrambling liana, up to 20–30 m long, main stem up to 25 cm in diameter. Branches obtusely quadrangular, generally puberulous. Stipules widely ovate-triangular, minutely and densely puberulous outside. Leaves opposite, petiolate; petioles 1.0–1.5 cm long, minutely puberulous or hirtellous; leaf blades ovate to ovate-oblong, 6.0–14.5 cm long, 2.5–8.5 cm wide; apex obtuse to acuminate; base rounded or subtruncate or subcordate; margin entire or occasionally crenulate in the upper half, glabrous or subglabrous above except strigillose on veins, area between veins densely

puberulent to subglabrous beneath; lateral veins six to ten pairs, level above, prominent beneath, tertiary veins distinct. Spines strongly recurved, tomentose in younger branches, glabrous in older ones. Inflorescences thyrsic with three to nine nodes, lateral units with one to eight pseudo-heads, the bracts reduced; heads small, 12–20 mm in diameter; peduncles densely hirtellous, 1.5–4 cm long. Flowers sessile; calyx tubular, 0.5–0.8 mm long with the obtuse lobes 0.2–0.3 mm long, densely villosulous outside, densely sericeous inside at the base; corolla densely retrorsely adpressed, puberulous outside, glabrous inside, tubes 3.5–5.0 mm long, 0.7–0.8 mm wide at the base, 1.0 mm wide at the mouth, lobes suborbicular, rounded, 1–1.5 mm long, 1–1.5 mm wide. Stamens five, some sterile; anthers 1.0–1.5 mm long, obtuse at the apex, prolonged and attenuated at the base; filaments around 0.2 mm long. Ovary 1.4–1.6 long, 0.9–1.3 mm wide, densely villosulous, style 6.5–9 mm long, glabrous; stigma 1.0 mm long, clavate. Capsules 0.8–1.2 cm long, pubescent outside; seeds with two long narrow wings, one bifid, 3.4 mm long (*6, 8–10*).

Plant material of interest: dried stem bark

General appearance

Shavings or chopped stem bark contain numerous bast fibres up to 7 cm long, fibre bundles and fine-crumbling rind/bark breaking into pieces. The sawdust-like chopped stem bark consists of wood fibres up to 1 cm long with a small fraction of short bast fibres and traces of powdered bark (*4*).

Organoleptic properties

No characteristic odour or taste (*4*).

Microscopic characteristics

Rings dark, partly elevated, but hardly structured. Under illumination, bast fibres show net-like or reticulate structure; with illumination from above, they glimmer with a brownish shimmer. Powdered stem bark consists of finely broken pieces of wood, bast and bark, and clear, crystalline particles of dried sap (*4*).

Powdered plant material

To be established in accordance with national requirements.

General identity tests

Macroscopic and microscopic examinations (*1, 4*), thin-layer chromatography (*4, 11*), and high-performance liquid chromatography for the presence of characteristic oxindole alkaloids (*4, 12, 13*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*14*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*15*). For other pesticides, see the European pharmacopoeia (*15*) and the WHO guidelines on quality control methods for medicinal plants (*14*) and pesticide residues (*16*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*14*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*14*) for the analysis of radioactive isotopes.

Other purity tests

Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, water-soluble extractive, alcohol-soluble extractive and loss on drying tests to be established in accordance with national requirements.

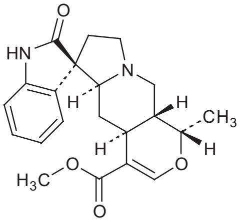
Chemical assays

Not more than 0.02% total tetracyclic oxindole alkaloids determined by high-performance liquid chromatography (*4, 12, 13*).

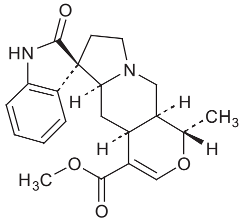
Major chemical constituents

The major constituents are indole alkaloids (0.15–4.60%), primarily pentacyclic oxindoles. The principal pentacyclic oxindole alkaloids are pteropodine, isopteropodine, speciophylline, uncarine F, mitraphylline and isomitraphylline. Tetracyclic oxindoles present include isorhynchophylline and rhynchophylline (*1, 4, 5, 12, 17*). The structures of the major pentacyclic oxindole alkaloids are presented below.

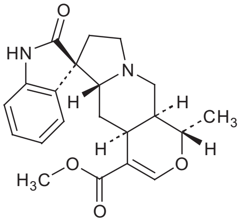
mitraphylline



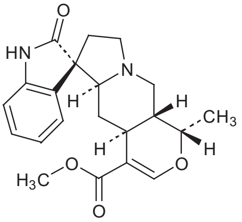
pteropodine



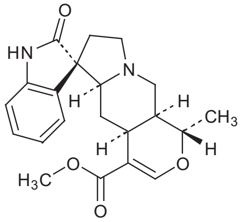
uncarine F



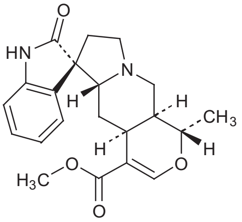
isomitraphylline



isopteropodine



speciophylline



Medicinal uses

Uses supported by clinical data

None. Although two clinical studies have suggested that Cortex Uncariae may be an immunostimulant and increase the number of white blood cells (*18, 19*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

Symptomatic treatment of arthritis, rheumatism and gastric ulcers (*7, 10, 20*).

Uses described in traditional medicine

Treatment of abscesses, asthma, fevers, urinary tract infections, viral infections and wounds. As an emmenagogue (*4, 5, 21*).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity

Addition of an undefined extract of the stem bark to the cell medium at a concentration of 100 µg/ml significantly attenuated ($P < 0.05$) peroxynitrite-induced apoptosis in HT29 (epithelial cells) and RAW 264.7 cells (macrophages). The extract further inhibited lipopolysaccharide-induced nitric oxide synthase gene expression (iNOS), nitrite formation, cell death, and the activation of nuclear transcription factor-κβ in RAW 264.7 cells. Oral administration of the extract in drinking-water, 5 mg/ml, attenuated indometacin-enteritis in rodents as evidenced by reduced myeloperoxi-

dase activity, morphometric damage and liver metallothionein expression (*22*).

The anti-inflammatory activities of two types of extracts from the stem bark: a hydroalcoholic extract containing 5.61% alkaloids (mainly of the pentacyclic type, extract A) and an aqueous freeze-dried extract containing 0.26% alkaloids (extract B) were assessed in the carrageenan-induced rat paw oedema test. Extract A was significantly more active than extract B, suggesting that the effect could be due to the presence of pentacyclic oxindole alkaloids. Both extracts showed little inhibitory activity on cyclooxygenase-1 and -2. Only a slight inhibitory activity on DNA-binding of NF-κB was observed (*23*).

The effects of a decoction of the stem bark, 10.0 μg/ml freeze-dried, on tumour necrosis factor-α (TNF-α) production and cytotoxicity in lipopolysaccharide-stimulated murine macrophages (RAW 264.7 cells) was assessed in vitro. The decoction prevented oxidative- and ultraviolet irradiation-induced cytotoxicity. It also suppressed TNF-α production by approximately 65–85% ($P < 0.01$) at concentrations of 1.2–28.0 ng/ml (*24*).

Cinchonain Ib, a procyanidin from the stem bark, inhibited the activity of 5-lipoxygenase, ≥ 100% at 42.5 μmol/ml, indicating an anti-inflammatory effect (*25*).

Antitumour activity

Growth inhibitory activities of an aqueous extract of the stem bark were examined in vitro using two human leukaemic cell lines (K562 and HL60) and one human Epstein–Barr virus-transformed B lymphoma cell line (Raji). Cell proliferation of HL60 and Raji cells was strongly suppressed in the presence of the aqueous extract, while K562 was more resistant to the inhibition. The suppressive effect was mediated through induction of apoptosis, which was shown by characteristic morphological changes, internucleosomal DNA fragmentation after agarose gel electrophoresis and DNA fragmentation quantification. The extract also induced a delayed type of apoptosis becoming most dose-dependently prominent after 48 hours of exposure. Both DNA single- and double-strand breaks were increased 24 hours following treatment (*26*). Leukaemic HL60 and U-937 cells were incubated with pure alkaloids from *U. tomentosa* root. The pentacyclic oxindole alkaloids inhibited the growth, median inhibitory concentration (IC_{50}) 10^{-5}–10^{-4} mol/l; the most pronounced effect was found for uncarine F. Selectivity between leukaemic and normal cells was observed (*13*).

Immune stimulating activity

Addition of 1 μmol/l of pentacyclic oxindole alkaloids (POA) induced endothelial cells to release some as yet to be determined factor(s) into the

supernatant, which enhanced the proliferation of normal human resting or weakly activated B and T lymphocytes. In contrast, proliferation of normal human lymphoblasts and of both the human lymphoblastoid B cell line Raji and the human lymphoblastoid T cell line Jurkat was inhibited, while cell viability was not affected. However, it was shown that the tetracyclic oxindole alkaloids had antagonistic effects to the POA, and dose-dependently reduced the proliferation of lymphocytes stimulated by POA (*27*).

Two commercial extracts of the stem bark, containing approximately 6 mg/g total oxindoles were assessed for the ability to stimulate the production of interleukin-1 (IL-1) and interleukin-6 (IL-6) in alveolar macrophages. A phosphate-buffered saline solution of the extracts stimulated IL-1 and IL-6 production by rat macrophages in a dose-dependent manner in the concentration range 0.025–0.1 mg/ml. In lipopolysaccharide (LPS)-stimulated macrophages, the extracts potentiated the stimulating effects of LPS on IL-1 and IL-6 production indicating an immune stimulating effect (*20*).

The immune effects of an aqueous stem bark extract were assessed after intragastric administration of the extract, 5.0–80.0 mg/kg body weight (bw) per day for 8 consecutive weeks. Phytohaemagglutinin (PHA)-stimulated lymphocyte proliferation was significantly ($P < 0.05$) increased in splenocytes of rats treated at doses of 40.0 mg/kg bw and 80.0 mg/kg bw. White blood cells from the groups treated with 40.0 mg/kg bw and 80.0 mg/kg bw per day for 8 weeks or 160.0 mg/kg bw per day for 4 weeks were significantly elevated ($P < 0.05$) as compared with controls. Repair of DNA single- and double-strand breaks 3 hours after 12 whole body irradiations were also significantly improved ($P < 0.05$) in rats treated with the stem bark (*19*).

Aqueous extracts of the stem bark, depleted of indole alkaloids (< 0.05%, w/w), were assessed for the treatment of chemically-induced leukopenia in rats. The animals were treated first with doxorubicin (DXR), three intraperitoneal injections of 2 mg/kg bw given at 24-hour intervals, to induce leukopenia. Beginning 24 hours after the last DXR treatment, the rats received 80 mg/kg bw of the aqueous extract per day by intragastric administration for 16 days. Animals treated with the extract recovered significantly sooner ($P < 0.05$) than those receiving DXR alone, and all fractions of white blood cells were proportionally increased. The mechanism of action on white blood cells is not known; however, data showing enhanced effects on DNA repair and immune cell proliferative response support a general immune enhancement (*28*).

Intraperitoneal administration of 10.0 mg/kg bw of an oxindole alkaloid-enriched extract of the stem bark enhanced phagocytosis in mice as assessed by the clearance of colloidal carbon. However, the pure alkaloids were not active without the presence of catechins such as the catechin tannin fraction of the root (*29*). In vitro, alkaloids from the stem bark were tested in two chemoluminescence models (granulocyte activation, phagocytosis) for their ability to enhance phagocytotic activity. Isopteropodine showed the strongest activity (55%), followed by pteropodine, isomitraphylline and isorhynchophylline (*29*).

Toxicity

The median lethal and toxic dose of a single oral dose of an aqueous extract of the stem bark in rats was > 8.0 g/kg bw. Although the rats were treated daily with aqueous extracts at doses of 10–80 mg/kg bw for 8 weeks or 160 mg/kg bw for 4 weeks, no symptoms of acute or chronic toxicity were observed. In addition, no changes in body weight, food consumption and organ weight, or kidney, liver, spleen and heart pathological changes were found to be associated with treatment (*19*).

Aqueous extracts of the stem bark were analysed for the presence of toxic compounds in Chinese hamster ovary cells and bacterial cells (*Photobacterium phosphoreum*) in vitro. At concentrations of 10.0–20.0 mg/ml, the extracts were not cytotoxic (*30*).

Clinical pharmacology

Immune stimulating activity

In a human volunteer study, an aqueous extract of the stem bark was administered to four healthy volunteers daily at a dose of 350.0 mg/day for 6 consecutive weeks. No side-effects were reported as judged by haematology, body weight changes, diarrhoea, constipation, headache, nausea, vomiting, rash, oedema or pain. A significant increase ($P < 0.05$) in the number of white blood cells was observed after 6 weeks of treatment (*19*).

Oral administration of two doses of 350 mg of an extract of the stem bark containing 0.05% oxindol alkaloids and 8–10% carboxy alkyl esters per day to human volunteers stimulated the immune system, as evidenced by an elevation in the lymphocyte/neutrophil ratios of peripheral blood and a reduced decay in 12 serotype antibody titre responses to pneumococcal vaccination at 5 months (*18*).

Adverse reactions

No information available.

Contraindications

Owing to its traditional use as an emmenagogue, Cortex Uncariae is contraindicated during pregnancy.

Warnings

No information available.

Precautions

Drug interactions

Commercial extracts of the stem bark inhibited the activity of human cytochrome P450, $IC_{50} < 1\%$. Cortex Uncariae should only be taken in conjunction with prescription drugs metabolized via cytochrome P450, such as protease inhibitors, warfarin, estrogens and theophylline under the supervision of a health-care provider (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

No information available.

Pregnancy: non-teratogenic effects

See Contraindications.

Nursing mothers

Owing to the lack of safety data, the use of Cortex Uncariae during nursing is not recommended, unless under the supervision of a health-care provider.

Paediatric use

Owing to the lack of safety data, the use of Cortex Uncariae in children under the age of 12 years is not recommended, unless under the supervision of a health-care provider.

Other precautions

No information available on general precautions or precautions concerning drug and laboratory test interactions; and teratogenic effects in pregnancy.

Dosage forms

Dried stem bark for infusions and decoctions, and extracts. Capsules and tablets. Store in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)
Average daily dose: extracts, 20.0–350.0 mg (*10, 19*). Capsules and tablets: 300.0–500.0 mg, one capsule or tablet two to three times.

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Fructus Zizyphi

Definition

Fructus Zizyphi consists of the dried ripe fruits of *Zizyphus jujuba* Mill. (*1*)[1] or *Z. jujuba* var. *inermis* Rehd. (Rhamnaceae) (*1–5*).

Synonyms

Rhamnus ziziphus L., *Zizyphus mauritiana* Lam., *Z. sativa* Gaertn., *Z. vulgaris* Lam., *Z. vulgaris* Lam. var. *inermis* Bunge, *Z. zizyphi* Karst. (*5–8*).

Selected vernacular names

Annab, badari, bayear, ber, black date, bor, borakoli, borehannu, brust-beeren, Chinese date, Chinese jujube, common jujube, da t'sao, desi ber, hei zao, hong zao, ilandai, jujube, jujube date, jujube plum, kamkamber, koli, kul, kul vadar, lanta, lantakkura, narkolikul, natsume, onnab, phud sa chin, red date, regi, spine date, unnab, vadai, vadar, vagari, zao (*1–3, 5–12*).

Geographical distribution

Indigenous over a wide area, from Southern Europe to South-East and East Asia. Cultivated in China, India, Japan and Republic of Korea (*5, 9–11*).

Description

A spiny, deciduous shrub or a small tree, up to 10 m high; spines in groups of two, one straight, up to 2.5 cm long and one curved. Leaves alternate, petiolate, oval-lanceolate, 2–7 cm long, 2.5–3.0 cm wide; apex slightly obtuse; base oblique; margin closely serrulate, with three veins. Inflorescence an axillary cyme. Flowers perfect, seven to eight in each cluster; calyx with cupuliform tube and five segments; petals five, yellow; disk lining the calyx tube; stamens five; ovary depressed into the disk. Fruits

[1] Included in the *Pharmacopoeia of the People's Republic of China* (*1*) as Fructus Jujubae.

are fleshy drupes, ovoid or oblong, 1.5–5.0 cm long, dark reddish brown when ripe (*7, 9, 10*).

Plant material of interest: dried ripe fruits

General appearance

Ellipsoidal or broad ovoid, 2–3 cm long, 1–2 cm in diameter; externally reddish brown with coarse wrinkles, or dark greyish red with fine wrinkles, lustrous; both ends slightly dented, with a scar of style at one end and a scar of peduncle at the other; epicarp thin and leathery; mesocarp thick, dark greyish brown, spongy, soft and adhesive; endocarp extremely hard, fusiform and divided into two loculi; seeds flat and ovoid (*1, 3, 4*).

Organoleptic properties

Odour: slightly aromatic; taste: sweet (*1, 3, 4*).

Microscopic characteristics

To be established according to national requirements.

Powdered plant material

To be established according to national requirements.

General identity tests

Macroscopic examination (*1, 3, 4*) and thin-layer chromatography (*1, 5*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 1.0% (*5*).

Total ash

Not more than 2.0% (*1*).

Acid-insoluble ash

Not more than 4.0% (*4*).

Water-soluble extractive

Not less than 17.0% (*4*).

Alcohol-insoluble extractive
Not less than 19.0% (*4*).

Loss on drying
Not more than 10.0% (*4*).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

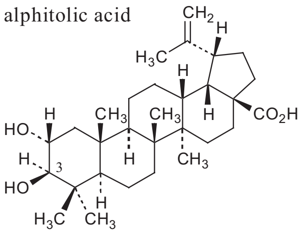
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests
Chemical tests to be established in accordance with national requirements.

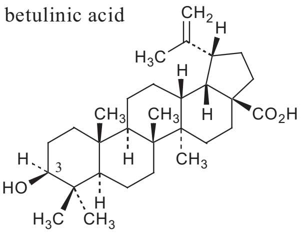
Chemical assays
Qualitative and quantitative high-performance liquid chromatography for the presence of 3-*O*-*trans*- and 3-*O*-*cis*-*p*-coumaroylalphitolic acid (*16*), and jujubosides A and B (*17*).

Major chemical constituents
Major characteristic constituents are triterpenes and triterpene saponins, including alphitolic, betulinic, maslinic, oleanolic, ursolic, 3-*O*-*trans*-alphitolic, 3-*O*-*cis*-*p*-alphitolic alphitolic, 3-*O*-*cis*-*p*-coumaroylalphitolic, and 3-*O*-*trans*-*p*-coumaroylalphitolic acids; and zizyphus saponins I, II, III, jujuboside B, spinosin and swertisin (*12, 18–22*). Three triterpene oligoglycosides, jujubosides A1 and C, and acetyljujuboside B have been isolated from the seeds (*23, 24*). Also present in the fruit are the biologically active compounds cyclic AMP and cyclic GMP (*25*), with concentrations estimated at 100–500.0 nmol/g and 30–50.0 nmol/g, respectively (*26*). A polysaccharide named ziziphus-arabinan has also been isolated from the fruit (*27*). The structures of representative triterpene and saponins are presented below.

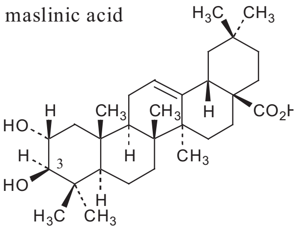
alphitolic acid

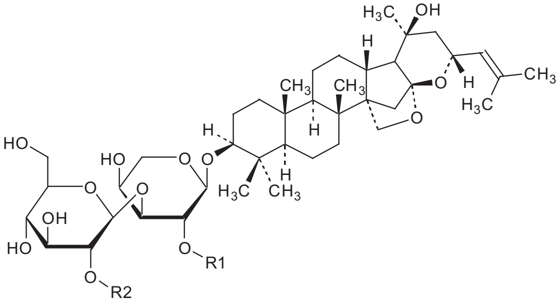


betulinic acid



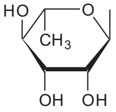
maslinic acid





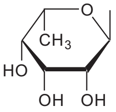
	R1	R2
jujuboside B	Rha	Xyl
zizyphus saponin I	dTal	H
zizyphus saponin II	Rha	H
zizyphus saponin III	dTal	Xyl

Rha =



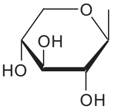
6-deoxy-α-L-mannopyranosyl

dTal =



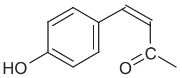
6-deoxy-α-L-talopyranosyl

Xyl =

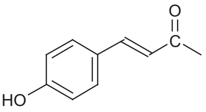


β-D-xylopyranosyl

cis-*p*-coumaroyl



trans-*p*-coumaroyl



Medicinal uses

Uses supported by clinical data

None. Although one uncontrolled human study has suggested that Fructus Zizyphi may be of some benefit for the treatment of insomnia (*28*), data from controlled clinical trials are lacking.

Uses described in pharmacopoeias and well established documents

To promote weight gain, improve muscular strength, and as an immunostimulant to increase physical stamina. Treatment of insomnia due to irritability and restlessness (*1*).

Uses described in traditional medicine

As an antipyretic, diuretic, emmenagogue, expectorant, sedative and tonic. Treatment of asthma, bronchitis, diabetes, eye diseases, inflammatory skin conditions, liver disorders, scabies, ulcers and wounds (*12*, *29*).

Pharmacology

Experimental pharmacology

Antiallergenic activity

Intraperitoneal injection of 100.0 mg/kg body weight (bw) of a 100% ethanol extract of the Fructus Zizyphi or the active constituent of the ethanol extract, ethyl α-D-fructofuranoside, daily for 5 days, inhibited haemagglutination-induced anaphylaxis in rats (*30*). A saline extract (0.85% sodium chloride) of the fruits (concentration not specified) prevented hypotonic and heat stress-induced haemolysis of erythrocyte membranes in vitro (*31*). Three triterpene oligoglycosides, jujubosides A1 and C, and acetyljujuboside B, in varying concentrations inhibited histamine release from rat peritoneal exudate cells induced by antigen–antibody reaction (*23*).

Anti-inflammatory activity

A methanol extract of the fruits, 0.1 mg/ml, did not suppress interleukin-8 induction in lipopolysaccharide-activated rat macrophages in vitro (*32*). A polysaccharide isolated from an aqueous extract of the fruits, Ziziphus-arabinan, 500.0 µg/ml, had anti-complementary activity in human serum in vitro (*27*). Both the *n*-butanol and diethyl ether extracts of the seeds exhibited anti-inflammatory activity in vitro as assessed by the albumin-stabilizing assay (*33*).

Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats daily for 4 days, produced a significant inhibition of carrageenan-induced footpad oedema (50.0% reduction, $P < 0.05$), and cotton pellet-induced granulomas (25.0% reduction, $P < 0.05$) (*29*).

Analgesic activity

A hot aqueous extract of the fruits did not inhibit conduction in the frog sciatic nerve when added to the bath medium at a concentration of 2.0% (*34*). Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to mice reduced the responsiveness of mice in the hot-plate and tail-flick tests, thereby demonstrating analgesic effects (*29*).

Antihyperglycaemic activity

Intragastric administration of a single dose of 1.0 g/kg bw of a 95% ethanol extract of the dried seeds suspended in water lowered the mean blood glucose concentrations in rabbits with alloxan-induced diabetes (*35*).

CNS depressant activity and toxicity

Chronic administration of 100.0 mg/kg bw of a 95% ethanol extract of the fruits to mice in drinking-water daily for 3 months had no effects on mortality, haematology, organ weight or sperm production (*29*). Intragas-

tric administration of an aqueous extract of the fruits, three doses of 0.5 mg/kg bw, 1.0 mg/kg bw or 3.0 mg/kg bw over 24 hours, to mice had no acute toxic effects (*29*). Intragastric administration of a 95% ethanol extract of the fruits, three doses of 1.0 g/kg bw over 24 hours, had no acute toxic effects. However, sedation was noted in animals treated with three doses of 3.0 g/kg bw (*29*).

Subcutaneous administration of 500.0 mg/kg bw of an aqueous extract of the seeds daily to mice depressed central nervous system activity, as measured by the potentiation of hexobarbital-induced sleeping time and antagonism of caffeine-induced hyperactivity (*36*). However, intraperitoneal administration of 500.0 mg/kg bw of a 75% methanol extract of the seeds to mice failed to have any effect on barbiturate-induced sleeping time (*37*). A saponin fraction of a defatted seed extract potentiated barbiturate-induced sleeping time when administered by intraperitoneal injection, 50.0 mg/kg bw (*38, 39*). Intraperitoneal and intragastric administration of up to 1.0 g/kg of a butanol, methanol or alkaloid-enriched fraction of a methanol extract of the fruits had tranquillizing effects in mice (*37, 40*). Intraperitoneal administration of 500.0 mg/kg bw of the flavonoids spinosin and swertisin, isolated from a petroleum ether extract of the dried seeds, had mild CNS-depressant effects in mice and potentiated hexobarbital-induced sleeping time by 50% (*39*).

An aqueous extract of the fruits, 100.0 mg/kg bw per day, administered to mice in the drinking-water for 3 months reduced average weight gain when compared with the controls (no extract). Two mice developed alopecia of the snout, one was anaemic and one was suffering from protrusion of the penis (*29*). The mortality rate compared to control animals was not significantly different, and there were no significant haematological changes ($P > 0.05$). Intragastric administration of 50.0 g/kg bw of a decoction of the fruits to mice had no toxic effects (*41*). No deaths occurred in mice given an aqueous extract of the fruits (15 g). The intraperitoneal median lethal dose (LD_{50}) of the decoction was 14.3 g/kg bw in rats. Subcutaneous administration of 10–15.0 g/kg bw of a 50% ethanol extract of the seeds to mice killed all animals within 30–60 minutes (*41*).

Immune stimulation

A purified polysaccharide, 0.5 mg/ml, isolated from an aqueous extract of the fruits, had anti-complement activity in human serum in vitro (*27*). Intragastric administration of 1.0 g/kg bw of a polysaccharide-enriched fraction from an aqueous extract of the fruits to mice enhanced the activity of natural killer cells (*42*).

Platelet aggregation inhibition
A hexane and 90% methanol extract of the dried seeds, 5.0 mg/ml, inhibited collagen-induced platelet aggregation in vitro (*43*).

Clinical pharmacology
Fructus Zizyphi is often a constituent in multicomponent prescriptions used in Kampo and traditional Chinese medicine. Numerous clinical trials have assessed the effects of the fruits in combination with other medicinal plants for anticonvulsant effects, memory-enhancing effects and anti-inflammatory effects. However, a review of these trials is beyond the scope of this monograph, and is therefore not included.

In one uncontrolled study, oral administration of the dried seeds to human subjects produced CNS depressant effects, and was reported to be effective for the treatment of insomnia at a dose of 0.8 g/day (*28*). No further details of this study are available.

Adverse reactions
No information available.

Contraindications
No information available.

Warnings
No information available.

Precautions
Carcinogenesis, mutagenesis, impairment of fertility
An aqueous and a methanol extract of the fruits were not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 or the *Bacillus subtilis* recombination assay at concentrations up to 100.0 mg/ml (*44*). A 70% ethanol extract of the fruits, up to 4.0 mg/ml, was not mutagenic in either the SOS-chromotest (*Escherichia coli* PQ37) or the SOS-umu test (*Salmonella typhimurium* TA1535) (*41*).

Intragastric administration of 1.0 g of the fruits per day to rats for 15 months inhibited the growth of adenocarcinomas of the stomach induced by *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (*45*). Administration of a 95% ethanol extract of the fruits in drinking-water, average daily dose 100 mg/kg bw, to mice for 3 months had no significant spermatotoxic effects (*29*).

Other precautions
No information available on general precautions or on precautions concerning drug interactions; drug and laboratory test interactions; teratogenic or non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.

Dosage forms
Dried fruits, aqueous and hydroalcoholic extracts. Store in a tightly sealed container away from heat and light.

Posology
(Unless otherwise indicated)
Daily dose: fruits 6–15 g (*1*).

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Annex 1

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* It was a great sorrow to learn of the death of Professor Fitak in February 2002. He had been working with Traditional Medicine, WHO, Geneva and supporting its projects for many years, especially the development of Volumes 1–3 of the ***WHO monographs on selected medicinal plants.*** His great contributions to WHO's work will always be remembered.

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Annex 2

Cumulative index

(in alphabetical order of plant name)

For the convenience of users of Volume 3, the monographs described in Volumes 1 and 2 are also listed in this index. The numbers printed in bold type, preceding the page numbers, indicate the volume in which the indexed item is to be found. Monographs are listed in alphabetical order of the plant name.

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Annex 3

Cumulative index
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For the convenience of users of Volume 3, the monographs described in Volumes 1 and 2 are also listed in this index. The numbers printed in bold type, preceding the page numbers, indicate the volume number in which the indexed item is to be found. Monographs are listed in alphabetical order of the plant material of interest.

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Selected WHO publications of related interest

Information on medicinal plants:

WHO monographs on selected medicinal plants, Volume 2
(ISBN 92 4 154537 2), 2002

WHO monographs on selected medicinal plants, Volume 1
(ISBN 92 4 154517 8), 1999

Quality assurance and control of herbal medicines:

WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants
(ISBN 92 4 154627 1), 2003

Quality control methods for medicinal plant materials
(ISBN 92 4 154510 0), 1998

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms
(ISBN 92 4 154513 5), 1998

Good manufacturing practices: Updated supplementary guidelines for the manufacture of herbal medicines, Annex 3 of WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-fourth report
(ISBN 92 4 120937 2), WHO Technical Report Series, No. 937, 2006

Regulation, evaluation and safety monitoring of herbal medicines:

Summary report of the global survey on national policy on traditional medicine and complementary/alternative medicine and regulation of herbal medicines
(ISBN 92 4 159323 7), 2005

WHO guidelines on safety monitoring and pharmacovigilance of herbal medicines
(ISBN 92 4 159221 4) , 2004

General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine
WHO/EDM/TRM/2000.1, 2000

Consumer information:

WHO guidelines on development of consumer information on proper use of traditional medicine and complementary/alternative medicine
(ISBN 92 4 159170 6), 2004

Further information on WHO technical documents in the field of traditional medicine including those listed above, can be found at the address below:
http://www.who.int/medicines/areas/traditional/

WHO published Volume 1 of the *WHO monographs on selected medicinal plants*, containing 28 monographs, in 1999, and Volume 2 including 30 monographs in 2002. This third volume contains an additional collection of 32 monographs describing the quality control and use of selected medicinal plants.

Each monograph contains two parts, the first of which provides pharmacopoeial summaries for quality assurance purposes, including botanical features, identity tests, purity requirements, chemical assays and major chemical constituents. The second part, drawing on an extensive review of scientific research, describes the clinical applications of the plant material, with detailed pharmacological information and sections on contraindications, warnings, precautions, adverse reactions and dosage. Also included are two cumulative indexes to the three volumes.

The *WHO monographs on selected medicinal plants* aim to provide scientific information on the safety, efficacy, and quality control of widely used medicinal plants; provide models to assist Member States in developing their own monographs or formularies for these and other herbal medicines; and facilitate information exchange among Member States. WHO monographs, however, are not pharmacopoeial monographs, rather they are comprehensive scientific references for drug regulatory authorities, physicians, traditional health practitioners, pharmacists, manufacturers, research scientists and the general public.

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